PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 21 February 2002 (21.02.02)	
International application No.: PCT/JP00/05503	Applicant's or agent's file reference:
International filing date: 17 August 2000 (17.08.00)	Priority date:
Applicant: OMURA, Satoshi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

04 September 2000 (04.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

_____

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

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Translation
10/088965

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION SeeNotificationofTransmittalofInternational Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/JP00/05503	International filing date (*day/month/year*) 17 August 2000 (17.08.00)	Priority date (*day/month/year*)
International Patent Classification (IPC) or national classification and IPC C07H 17/08 // A61K 31/7048, A61P 11/00, 29/00		
Applicant THE KITASATO INSTITUTE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04 September 2000 (04.09.00)	22 May 2001 (22.05.2001)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP00/05503

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☐ the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	3,4,5-20,22,23,27-34,36,40-52	YES
	Claims	1,2,21,24-26,35,37-39	NO
Inventive step (IS)	Claims		YES
	Claims	1-52	NO
Industrial applicability (IA)	Claims	1-52	YES
	Claims		NO

2. Citations and explanations

Document 1: EP, 838469, A (Solvay Pharmaceuticals GmbH), 29 April (29.04.98)

Document 2: EP, 550895, A1 (Kali-Chemie Pharma GmbH), 14 July 1993 (14.07.93)

Document 3: EP, 382472, A2 (Eli Lilly and Co.), 16 August 1990 (16.08.90)

Document 4: EP, 296717, A2 (Eli Lilly and Co.), 28 December 1988 (28.12.88)

Document 5: I. O. Kibwage et al., Identification of novel erythromycin derivatives in mother liquor concentrates of Streptomyces erythraeus", J. Antibiot., 1987, Vol. 40, No., pp. 1-6

Document 6: EP, 937734, A1 (Solvay Pharmaceuticals GmbH), 25 August 1999 (25.08.99)

Document 7: WO, 92/18134, A1 (Abbott Laboratories), 29 October 1992 (29.10.92)

Document 8: EP, 349100, A2 (Eli Lilly and Co.), 3 January 1990 (03.01.90)

Documents 1 and 2 disclose pseudoerythromycin derivatives which are inventions set forth in Claims 1, 2, 21 and 24 to 26 in the present application.

(See the compounds given Registry No. 151052-42-5, 151052-43-6 and 151122-18-8 in the CAplus database on STN,

American Chemical Society (ACS), (Columbus, OH), records DN.128:308701 and DN. 119:271625.)

Document 3 discloses pseudoerythromycin derivatives which are inventions set forth in Claims 35 and 37 to 39 in the present application.

(See the compounds given Registry No. 132201-81-1, 121590-61-2 and 132137-36-1 in the CAplus database on STN, American Chemical Society (ACS), (Columbus, OH), record DN.114:102696.)

Document 4 discloses pseudoerythromycin derivatives which are inventions set forth in Claims 1, 24 to 26, 35 and 37 to 39 in the present application.

(See the compounds given Registry No. 105882-69-7, 105882-72-2 and 121590-61-2 in the CAplus database on STN, American Chemical Society (ACS), (Columbus, OH), record DN.111:58271.)

Document 5 discloses pseudoerythromycin derivatives which are inventions set forth in Claims 1, 2 and 24 to 26 in the present application.

(See the compounds given Registry No. 107745-55-1 and 105882-69-7 in the CAplus database on STN, American Chemical Society (ACS), (Columbus, OH), record DN.106:172535.)

Document 6 discloses pseudoerythromycin derivatives which are inventions set forth in Claims 1 and 24 to 26 in the present application.

(See the compounds given Registry No. 236099-91-5 and 151052-42-5 in the CAplus database on STN, American Chemical Society (ACS), (Columbus, OH), record DN. 131:144790.)

Document 7 discloses pseudoerythromycin derivatives which are inventions set forth in Claims 1 and 24 to 26 in the present application.

(See the compounds given Registry No. 105882-69-7, 145692-88-2, 145692-89-3, 145692-94-0, 145692-95-1,

145692-97-3,145693-00-1,145693-01-2, 145693-02-3, 145693-03-4 and 145774-00-1 in the CAplus database on STN, American Chemical Society (ACS), (Columbus, OH), record DN. 118:101716.)

Document 8 discloses pseudoerythromycin derivatives which are inventions set forth in Claims 1 and 24 to 26 in the present application.

(See the compounds given Registry No. 105882-69-7, 127931-39-9 and 127966-89-6 in the CAplus database on STN, American Chemical Society (ACS), (Columbus, OH), record DN. 113:59777.)

Therefore, the inventions set forth in Claims 1, 2, 21, 24 to 26, 35 and 37 to 39 in the present application are not novel.

In addition, alteration of terminal substituent groups expected to have an equivalent effect is such as could be deduced easily by a person skilled in the art from the disclosures in Documents 1 to 8 here. Therefore, the inventions set forth in Claims 1 to 52 in the present application do not involve an inventive step.

The inventions set forth in Claims 1 to 52 in the present application are industrially applicable.

特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関
国際事務局

(43) 国際公開日
2002年2月21日 (21.02.2002)

PCT

(10) 国際公開番号
WO 02/14338 A1

(51) 国際特許分類[7]: C07H 17/08, A61K 31/7048 // A61P 11/00, 29/00

(21) 国際出願番号: PCT/JP00/05503

(22) 国際出願日: 2000年8月17日 (17.08.2000)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

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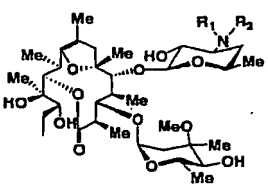
(81) 指定国 (国内): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) 指定国 (広域): ARIPO 特許 (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), ヨーロッパ特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI 特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

添付公開書類:
— 国際調査報告書

(54) Title: NOVEL PSEUDOERYTHROMYCIN DERIVATIVES

(54) 発明の名称: 新規シュードエリスロマイシン誘導体



[I]

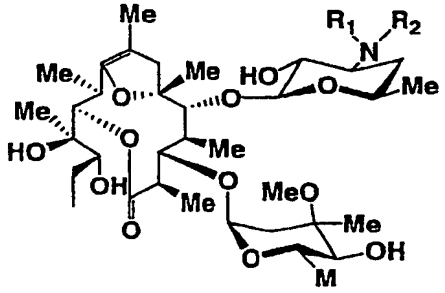
(57) Abstract: Pseudoerythromycin derivatives represented by the general formula [I] and serving as novel anti-inflammatory agents having decreased antibacterial activities and increased anti-inflammatory activities: [I] wherein R_1 and R¿2 ?are each independently H, alkyl, alkynyl, acyl, or sulfonyl, provided these groups may be each substituted; and Me is methyl.

[続葉有]

WO 02/14338 A1

(57) 要約:

本発明は、減少した抗菌活性と、増加した抗炎症作用を有する新たな抗炎症剤を得るものであって、下記一般式［Ｉ］



［Ｉ］

式中、R_1 及びR_2 は、同じかまたは異なり、それぞれH、アルキル、アルキニル、アシル、スルホニルを示し、これらは置換基を有していてもよい、Ｍｅはメチルで表されるシュードエリスロマイシン誘導体である。

明　細　書

新規シュードエリスロマイシン誘導体

発明の属する技術分野

本発明は新規シュードエリスロマイシン誘導体、またはその塩に関する。

従来の技術

エリスロマイシン（Ｅｒｙｔｈｒｏｍｙｃｉｎ；以下時としてＥＭと呼称する場合もある）は、１４員環マクロライド系抗生物質として、主としてグラム陽性菌による感染症の治療に長年用いられて来た。過去１０数年において、エリスロマイシンは細菌感染症に対する治療作用とは別に、びまん性汎細気管支炎や気管支喘息を含む長期慢性炎症性疾患を改善することが知られて来た。（工藤翔二ら、びまん性汎細気管支炎に対するエリスロマイシン少量長期投与の臨床成績に関する研究－四年間の治療成績、日胸疾会誌２５：６３２－６４２、１９８７）。

発明が解決しようとする課題

エリスロマイシンは、抗生物質であるので、炎症性疾患を治療するのに必ずしも必要とされない作用である抗菌作用を有している。そのため、投与された患者に、耐性菌が生じたり、それに伴って、別の機会に感染症をおこした際に、治療の障害となったりする問題が生じていた。

課題を解決するための手段

上記したように、びまん性汎細気管支炎がエリスロマイシンの少量長期投与によって改善されることが、工藤翔二ら（びまん性汎細気管支炎に対するエリスロマイシン少量長期投与の臨床成績に関する研究－四年間の治療成績、日胸疾会誌２５：６３２－６４２、１９８７）により明らかにされている。

近年、こうしたエリスロマイシンの抗生物質以外の作用が注目を集め、びまん性汎細気管支炎に限らず慢性副鼻腔炎やクローン病など、呼吸器科領域を越え

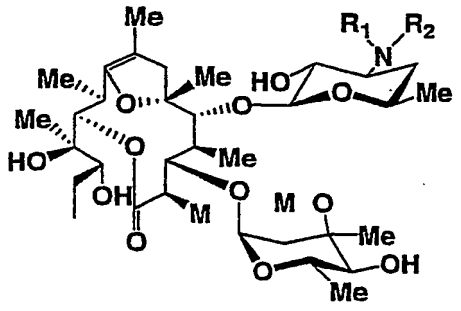
た分野での有用性が報告されはじめている。エリスロマイシンによるびまん性汎細気管支炎のような慢性疾患に対する作用機序は、本来の抗菌作用によるものでないと考えられている。目下、研究が進行中であるが、慢性気道炎症の場をとりまく免疫炎症細胞を介する抗炎症作用であることが示唆されている。

例えば、好中球に直接作用して感染部位への遊走を制御したり、またメディエイターやサイトカインなどを介して間接的に作用し、好中球遊走を制御したり、好中球からの活性酸素の放出を制御するとも言われている。更に、リンパ球、マクロファージ、肥満細胞にも作用し、その増殖やサイトカイン産生を制御したり、また分化を誘導する作用が報告されている。（炎症・免疫とマクロライドＵＰ　ＴＯ　ＤＡＴＥ、清水喜八郎、大村智監修、工藤翔二編、医薬ジャーナル社、大阪、１９９６）。

以上のように、１４員環マクロライドは免疫制御および抗炎症作用を示す結果、慢性呼吸器疾患を治癒するものと考えられている。

そこで、本発明者らは、エリスロマイシンの単球からマクロファージへの分化誘導促進作用（N. Keicho, S. Kudoh, H. Yotsumoto, K. Akagawa, Erythromycin promotes monocyte to macrophage differentiation, J. Antibiotics, 47, 80－89, 1994）に着目して、抗菌活性が消失し、しかも分化誘導促進作用の増強した誘導体の創製を目的にエリスロマイシン誘導体を合成することとした。

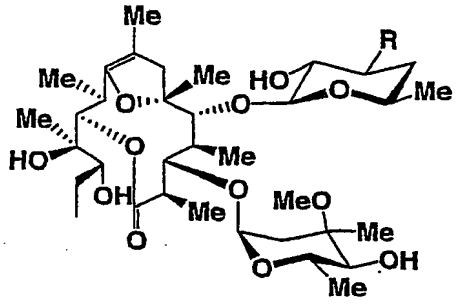
即ち、本発明は、下記一般式［Ｉ］



［Ｉ］

式中、R_1 およびR_2 は、同じかまたは異なり、それぞれH，アルキル、アルキニル、アシル、スルホニルを示し、これらは置換基を有していてもよい、Ｍｅはメチルで表される新規シュードエリスロマイシン誘導体に関する。

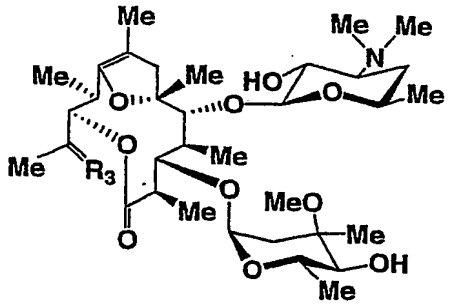
更に本発明は、下記一般式［II］



［II］

式中、Ｒは、Ｎを含むヘテロ環を示し、これらは置換基を有していてもよい、Ｍｅはメチル、で表される新規シュードエリスロマイシン誘導体に関する。

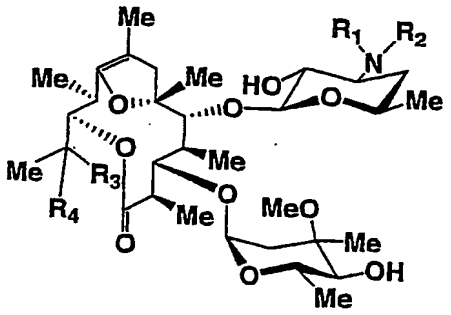
更に本発明は、下記一般式［Ⅲ］



［Ⅲ］

式中、R_3 はＯまたはＮＯＨ、Ｍｅはメチルを示す、で表される新規シュードエリスロマイシン誘導体に関する。

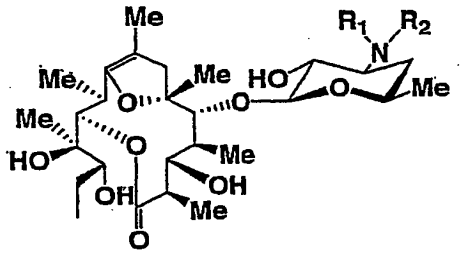
更に本発明は、下記一般式［Ⅳ］



［Ⅳ］

式中、R_1 およびR_2 は、同じかまたは異なり、それぞれH、メチルを示し、R_3 およびR_4 は、それぞれH、水酸基、アミノ基、Meはメチルを示す、で表される新規シュードエリスロマイシン誘導体に関する。

更に本発明は、下記一般式［V］



［V］

式中、R_1 およびR_2 は、同じかまたは異なり、それぞれH、メチル、Meはメチルを示す、で表される新規シュードエリスロマイシン誘導体に関する。

各種エリスロマイシン誘導体の合成法としては、例えば、第１図の合成スキームに示すようにして合成した。即ち、エリスロマイシンAを文献（a）I. O. Kibwage, R. Busson, G. Janssen, J. Hoogmartens, H. Vanderhaeghe, Translactonization of Erythromycins, J. Org. Chem., 52, 990－996, 1987、（b）H. A. Kirst, J. A. Wind, J. W. Paschal, Synthesis of Ring－Constracted Derivatives of Erythromycin, J. Org. Chem., 52, 4359－4362, 1987に従い、まず氷酢酸で処理して、エリスロマイシンA エノール エーテル（EM201）に導き、続いて炭酸カリウム存在下メタノール中加熱還流することにより、シュードエリスロマイシンA エノール エーテル（EM701）（公知化合物）に導いた。

続いて文献（L. A. Friberg, 米国特許第3, 725, 385号明細書）に従い、ヨウ素と酢酸ナトリウムで処理してデーNーメチルーシュードエリスロマイシンA エノール エーテル（EM703）（新規化合物）を得た。

更に、ヨウ素とナトリウムメトキシドで処理してビス（デーNーメチル）ーシュードエリスロマイシンA　エノール　エーテル（EM721）（新規化合物）を得た。EM703およびEM721を用いて、種々アルキル化、アシル化、スルホニル化をしてビスーデ（3'ーNーメチル）ー3'ーNーエチルー8，9ー無水ーシュードエリスロマイシンA　6，9ーヘミケタール（EM722）から誘導体を合成した。

本発明化合物の合成スキームの一例は第1図に示す。即ち、エリスロマイシンA（EMA）→エリスロマイシンA　エノール　エーテル（EM201）→シュードエリスロマイシンA　エノール　エーテル（EM701）→デーNーメチルーシュードエリスロマイシンA　エノール　エーテル（EM703）→ビス（デーNーメチル）ーシュードエリスロマイシンA　エノール　エーテル（EM721）の処理工程により得られる。

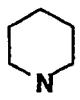
実施例に示す本発明化合物について分化誘導増強効果を確認するため、ヒト単球からマクロファージへの分化誘導増強作用を測定した。方法は以下の通りにして行った。

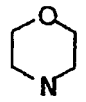
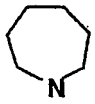
THPー1細胞培養液を遠心して集め、培地（RPMI　1640）で2×10^5 cell／mlの濃度に調整して、48穴プレートの各well に500μlづつ分注する。各well にPMA溶液10μlとサンプル溶液5μlを添加し、軽くゆすって攪拌後、37℃、CO_2 5%条件下で72ー96時間インキューベートする。更にMTT0．5mg／ml溶液を300μl／well 添加し、37℃、CO_2 5%条件下で3時間インキュベートする。注射筒を用いて上清のみを吸い上げ、連続分注機でDMSO500μlを添加し、フォルマザンを完全に溶解させ、100μlづつ96穴プレートに移す。これをプレートリーダを用いて、吸光度測定する。

以上の測定方法に従って測定したヒト単球からマクロファージへの分化誘導増強作用の結果は第1表に示す。

第１表

ＥＭ７０３類似誘導体の構造とＴＨＰ－１／Ｍφ系における活性結果

			その他	処理濃度（μM）					ED_{50}(μM)*
EM	R_1	R_2		0.3	1	3	10	30	100
703	Me	H		+	+	+	+	/	0.3
721	H	H		NT	NT	−	+	/	10
722	Et	H		−	+	+	++	/	1
723	Et	Et		−	+	+		/	1
724	アリル	H		−	+	+	++	/	1
725	アリル	アリル		NT	−	±	+	/	3
726	Ac	H		−	−	−	−	−	−
727	Ms	Me		−	+	+	+	/	1
728	$CH_2C\equiv CH$	H		−	+	+	+	+	1
729	$CH_2C\equiv CH$	$CH_2C\equiv CH$		−	±	±	±	/	1
730	Pr	H		+	+	+	/	/	0.3
731	Pr	Pr		−	−	+	/	/	3
732	Bn	H		+	+	+	+	/	0.3
733	Bn	Bn		−	±	±	/	/	1
734				−	±	+	+	/	1
735				−	±	+	++	/	1
736	i-Pr	H		−	±	+	++	/	1
737	Me	Me	decladinose	NT	NT	−	+	/	10
738	C_6H_{13}	H		−	±	+	/	/	1

739	C_6H_{13}	C_6H_{13}		−	±	+	+	/	1
740	C_2H_4F	Me		±	±	+	+	+	0.3
742	CH_2CN	Me		−	−	−	+	+	10
743	Me	Me	C12oxime	NT	−	±	−	/	−
744	C_3H_6OH	Me		NT	−	−	−	/	−
745	C_2H_4OAc	Me		−	−	++	++	++	3
746	Me	Me	C12MeCHOH	−	±	+	+	+	1
747				NT	NT	−	±	++	10
748				−	±	++	++	/	1
749	$(CH_2)_{10}Br$	$(CH_2)_{10}Br$		NT	±	+	+	/ 不溶	1
750	Me	Me	C12MeCHNH$_2$	NT	−	−	±	/	10
751	H	Me	C12MeCHOH	±	±	+	+	/	0.3
754	Me	H	decladinose	NT	−	−	NT	+	30
EM	Me	H		NT	−	±	+	+	3
CAM	Me	H		NT	NT	−	+	−	10
EM oxime									
	Me	Me	C9oxime	NT	−	±	±	++	3

第１表中、Ｍｅ：メチル、Ｐｒ：プロピル、Ｅｔ：エチル、Ａｃ：アセチル、およびＭｓ：メタンスルホニルをそれぞれ表す。＊ED_{50}：ＴＨＰがＭφに５０％分化誘導するのに必要な薬剤濃度（μＭ）を示すものである。

第１表中の活性表示は、ＥＭ１００μＭの分化誘導増強活性との比較で表したものであり、＋＋：１００％以上増強、＋：５０－１００％増強、±：２５－５０％増強、－：活性なし、／：細胞毒性を発現、ＮＴ：ｎｏｔ　ｔｅｓｔｅｄ又は評価中をそれぞれ意味する。

第１表に示す如く、ＥＤ$_{50}$値（μＭ）（ＴＨＰ－１からＭφへ５０％分化誘導するために必要な最小薬剤濃度）の数値が小さい程、化合物の分化誘導作用が強いことから、本発明の化合物はＴＨＰ－１からＭφへの分化誘導増強作用を有することが判った。

次に、本発明の化合物ＥＭ７０３について、ブレオマイシン［Ｂｌｅｏｍｙｃｉｎ（以下時として、ＢＬＭという）］の肺腺維症の抑制効果を調べた。

ＩＣＲマウス７週令を用いて、５％アラビアゴムに懸濁したサンプル５０ｍｇ／ｋｇ／ｄａｙを経口で１７日間（ｄａｙ－３～ｄａｙ１３）投与し、ｄａｙ０にブレオマイシン１００ｍｇ／ｋｇを尾静脈より投与する。そして、ｄａｙ２８に麻酔下にと殺し、サンプル非投与マウスと肺の繊維化の程度を比較した。抑制効果は第２表に示す。

参考文献：

Ａｚｕｍａ Ａ.，Ｆｕｒｕｔａ Ｔ.，Ｅｎｏｍｏｔｏ Ｔ.，Ｈａｓｈｉｍｏｔｏ Ｙ.，Ｕｅｍａｔｓｕ Ｋ.，Ｎｕｋａｒｉｙａ Ｎ.，Ｍｕｒａｔａ Ａ.，Ｋｕｄｏｈ Ｓ.，Ｐｒｅｖｅｎｔｉｖｅ ｅｆｆｅｃｔ ｏｆ ｅｒｙｔｈｒｏｍｙｃｉｎ ｏｎ ｅｘｐｅｒｉｍｅｎｔａｌ ｂｌｅｏｍｙｃｉｎ－ｉｎｄｕｃｅｄ ａｃｕｔｅ ｌｕｎｇ ｉｎｊｕｒｙ ｉｎ ｒａｔｓ Ｔｈｏｒａｘ ５３，１８６－１８９，１９９８

第２表

［投与スケジュール］

BLM100 mg/kg

↓

Day -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 28

EM703 50 mg/kg/day ↓

と殺

結果：組織中ハイドロキシプロリン濃度

群別		測定値（μmol/l）	重量換算値（μmol/g）
Ｃｏｎｔ		４４０	４．０
ＢＬＭ	１	７８５	７．１
ＢＬＭ	２	７３３	６．４
ＥＭ７０３	１	５５２	５．０
ＥＭ７０３	２	４８９	４．６
ＥＭ７０３	３	５９１	５．４
ＢＬＭ＋ＥＭ７０３	１	５８３	５．２
ＢＬＭ＋ＥＭ７０３	２	４９５	４．５
ＢＬＭ＋ＥＭ７０３	３	４３７	４．４
ＢＬＭ＋ＥＭ７０３	４	３１４	２．９
ＢＬＭ＋ＥＭ７０３	５		

群別：

Ｃｏｎｔ（対照）群（ｎ＝１）

ＢＬＭ（ブレオマイシン）群（ｎ＝２）

ＥＭ（エリスロマイシン）群（ｎ＝４）

ＢＬＭ（ブレオナイシン）＋ＥＭ（エリスロマイシン）７０３群（ｎ＝５）

以上の通り、ハイドロキシプロリンは、肺繊維化の指標で、高い数字が繊維化が高いことを示している。ＥＬＭ投与群における肺傷害のハイドロキシプロリン濃度はＢＬＭ＋ＥＭ７０３投与群において減少していた。

次に、化合物ＥＭ７０３について、インフルエンザウイルス感染による肺炎の抑制効果を調べた。

サンプルを１％ＤＭＳＯを含む生理食塩水で溶解し、マウスインフルエンザ肺炎モデルに対し、感染１～６日目までヒトの経口少量長期療法に相当する量（

0．3mg、0．03mg／mice）を1日1回腹腔内投与して、溶媒のみを投与した対象群を比較した。

参考文献：

Sato K.，Suga M.，Akaike T. et al：Therapeutic effect of erythromycin on influenza virus－induced lung injury in mice. Am. J. Respir Crit Care Med. 157，853－859，1998.

結果は、第2図および第3図に示した。この系では、マウスは肺炎を起こし、感染後20日ごろに殆どが死亡した。それに対して、第2図に示すように、EM703を0．3mg／mice投与することにより、肺炎が治癒され、40％のマウスが生存していた。また、第3図に示すように、薬剤未処理（対照）のものは、肺炎によりマウスの体重は著しく減少するが、EM703投与により10日目より体重増加を示した。このことから、肺炎の抑制効果が起こり、肺炎が治癒されたことを示す。

以上の通り、本発明化合物は、インフルエンザウイルス感染による肺炎の抑制効果を示す。

図面の簡単な説明

第1図は本発明化合物の合成スキームの一例を示したものである。

第2図は本発明の化合物について、インフルエンザウイルス感染による感染後日数と生存率との関係を示した肺炎の抑制効果のグラフである。

第3図は本発明の化合物について、ブレオマイシンの肺繊維症の抑制効果のグラフである。

実施例

次に参考例および実施例を挙げて、本発明を説明するが、本発明はこれら実施例のみに限定されるものではない。

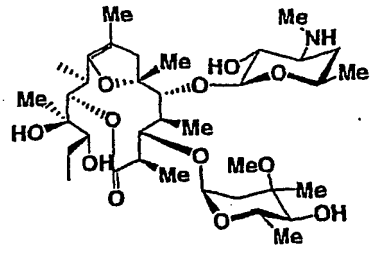
参考例１

ＥＭ７０１の合成

エリスロマイシン（１２．４ｇ，１６．９ｍｍｏｌ）の氷酢酸溶液を室温で２時間撹拌した後、炭酸水素ナトリウム水溶液をゆっくり加え、中和した。反応液は、クロロホルムで抽出し、有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルクロマトグラフイーで精製（クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５）して、ＥＭ２０１（７．７ｇ、６３％）を得た。続いてＥＭ２０１（７．６ｇ，１０．６ｍｍｏｌ）のメタノール溶液に炭酸カリウム（１．４ｇ、１０．６ｍｍｏｌ）を加え、２時間還流した。溶媒を留去後、残渣を炭酸水素ナトリウム水溶液に溶解し、クロロホルムで抽出した。芒硝で脱水し、ろ過・留去後、得られる粗物質を、シリカゲルカラムクロマトグラフイーで精製（クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５）して、標記の化合物ＥＭ７０１（５．９ｇ，７８％、白色粉末）を得た。

実施例１

デ（３’－Ｎ－メチル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７０３）の合成



EM703

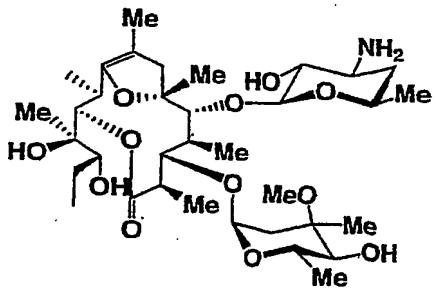
ＥＭ７０１（６．９ｇ，９．７ｍｍｏｌ）のメタノール（５２．０ｍＬ）－水（１３．０ｍＬ）溶液に、室温下、酢酸ナトリウム（３．９ｇ，４８．５ｍｍ

ｏ１）とヨウ素（２．５ｇ，９．７ｍｍｏｌ）を順に少量ずつ加えた後、５０℃に昇温して３時間撹拌した。その撹拌の間、１Ｎ水酸化ナトリウム水溶液を加え、ｐＨが常に８－９になるように調節した。ＴＬＣで反応終了を確認した後、反応液はアンモニア水（７．５ｍＬ）－水（２００ｍL）で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５］して、標記化合物ＥＭ７０３（４．８ｇ、収率７０％、白色粉末）を得た。

ＥＭ７０３：ｍ．ｐ．：１７７－１８０℃

実施例２

ビス－デ（３’－Ｎ－メチル）－８，９－無水－シュードエリスロマイシンＡ６，９－ヘミケタール（ＥＭ７２１）の合成



EM721

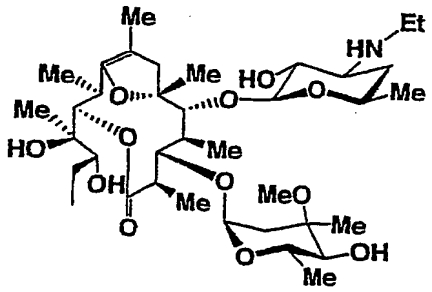
ナトリウム（４．５ｇ，１．６７ｍｍｏｌ）をメタノール（１５ｍＬ）に加え、ナトリウムメトキシドのメタノール溶液を調製した後、ＥＭ７０３（１９５．４ｍｇ，０．２７９ｍｍｏｌ）とヨウ素（３５３．６ｍｇ，１．３９３ｍｍｏｌ）を０℃下順次加え、３時間撹拌した。ＴＬＣで反応終了を確認した後、チオ硫酸ナトリウム（０．８ｇ）、アンモニウム水溶液（０．５ｍＬ）、そして水（８０ｍＬ）を加え、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロ

マトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５］して、標記化合物ＥＭ７２１（１６６．３ｍｇ、収率８７％、白色粉末）を得た。

ＥＭ７２１：ｍ．ｐ．：１３４－１３６℃；ＩＲ（ＫＢｒ）ν：３４６７．４，２９７３．７，２９３５．１，２８７９．２，１７００．９，１６３７．３，１４５７．９，１３８０．８，１２６５．１，１１６６．７，１１２６．２，１０７９．９，１０３７．５，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{35}H_{61}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$７１０．４０９１，実測値７１０．４０６０

実施例３

ビス－デ（３’－Ｎ－メチル）－３’－Ｎ－エチル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７２２）の合成



EM722

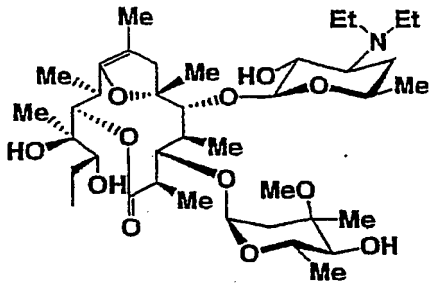
ＥＭ７２１（２１．０ｍｇ，０．０３０５ｍｍｏｌ）のジメチルホルムアミド（１．０ｍＬ）溶液にＮ，Ｎ－ジイソプロピルエチルアミン（２６．６μＬ，０．１５３ｍｍｏｌ）とヨウ化エチル（１２．２μＬ，０．１５３ｍｍｏｌ）を加え、室温で４時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５］して、標記化合物ＥＭ７２２（７．０ｍｇ、収率３

２％、白色粉末）を得た。

ＥＭ７２２：ｍ．ｐ．：１２４－１２６℃；ＩＲ（ＫＢｒ）ν：３４７１．６，２９３３．２，１７０４．８，１４５７．９，１３７８．９，１２６３．１，１１６６．７，１１２８．２，１０７４．２，１０３７．５，１０１８．２ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{37}H_{65}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$７３８．４４０４，実測値７３８．４３９３

実施例４

ビスーデ（３’－Ｎ－メチル）－３’，３’－Ｎ，Ｎ－ジエチル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７２３）の合成



EM723

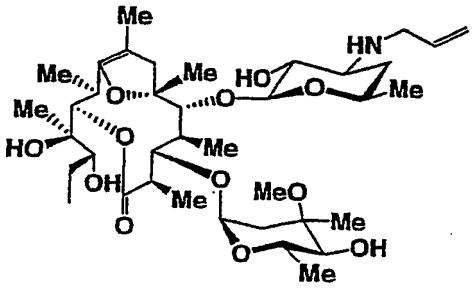
ＥＭ７２１（２１．０ｍｇ，０．０３０５ｍｍｏｌ）のジメチルホルムアミド（１．０ｍＬ）溶液にＮ，Ｎ－ジイソプロピルエチルアミン（２６．６μＬ，０．１５３ｍｍｏｌ）とヨウ化エチル（１２．２μＬ，０．１５３ｍｍｏｌ）を加え、室温で４時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５］して、標記化合物ＥＭ７２３（１０．３ｍｇ、収率４５％、白色粉末）を得た。

ＥＭ７２３：ｍ．ｐ．：１６５－１６８℃；ＩＲ（ＫＢｒ）ν：３４７３．７，２９３５．１，１６９９．０，１３８２．７，１３１７．１，１２６７．０

，１１６６．７，１１２６．２，１１０８．９，１０７８．０，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{39}H_{69}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$７６６．４７１７，実測値７６６．４７１０

実施例５

ビスーデ（３’－Ｎ－メチル）－３’－Ｎ－アリル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７２４）の合成



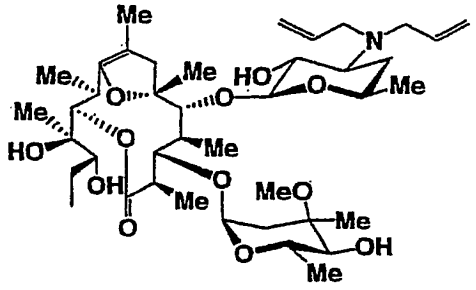
EM724

ＥＭ７２１（１１７．８ｍｇ，０．１７１ｍｍｏｌ）とＮ，Ｎ－ジイソプロピルエチルアミン（２９８．６μＬ，１．７１４ｍｍｏｌ）を加えたジクロロメタン（５．７ｍＬ）溶液に、０℃下、臭化アリル（１４８．３μＬ，１．７１４ｍｍｏｌ）を加え、室温に昇温後、２時間攪拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５］して、標記化合物ＥＭ７２４（２１．９ｍｇ、収率３０％、白色粉末）を得た。

ＥＭ７２４：ｍ．ｐ．：１０６－１０９℃；ＩＲ（ＫＢｒ）ν：３４４８．８，２９７１．８，２９３３．２，１７１８．３，１６３７．３，１３８０．８，１２６５．１，１１６６．７，１１２６．２，１０７８．０，１０３７．５，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{38}H_{65}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$７５０．４４０４，実測値７５０．４４２０

実施例６

ビス－デ（３’－Ｎ－メチル）－３’，３’－Ｎ，Ｎ－ジアリル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７２５）の合成



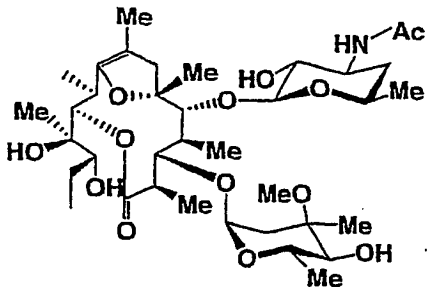
EM725

ＥＭ７２１（１１７．８ｍｇ，０．１７１ｍｍｏｌ）とＮ，Ｎ－ジイソプロピルエチルアミン（２９８．６μＬ，１．７１４ｍｍｏｌ）を加えたジクロロメタン（５．７ｍＬ）溶液に、０℃下、臭化アリル（１４８．３μＬ，１．７１４ｍｍｏｌ）を加え、室温に昇温後、２時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１→１０：１：０．０５］して、標記化合物ＥＭ７２５（６４．３ｍｇ、収率５９％、白色粉末）を得た。

ＥＭ７２５：ｍ．ｐ．：１４０－１４２℃；ＩＲ（ＫＢｒ）ν：３４７１．７，２９７１．８，２９２７．４，１７００．９，１６３７．３，１３８０．８，１３１７．１，１２６５．１，１１６６．７，１１２４．３，１１１４．７，１０４９．１，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{41}H_{69}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$ ７９０．４７１７，実測値７９０．４７１６

実施例７

ビス－デ（３’－Ｎ－メチル）－３’－Ｎ－アセチル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７２６）の合成



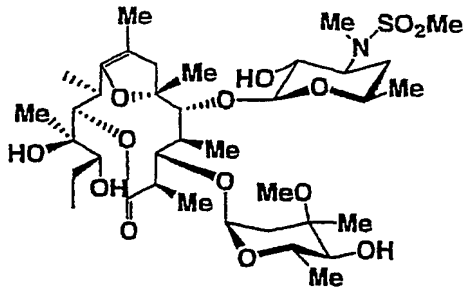
EM726

EM721（34．8mg，0．0506mmol）のジクロロメタン（1．6mL）溶液に、0℃下、無水酢酸（8．4μL，0．0759mmol）を加え、10分間撹拌した後室温へ昇温して、更に30分間撹拌した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール＝100：1→20：1］して、標記化合物EM726（33．4mg、収率91％、白色粉末）を得た。

EM726：m．p．：137－139℃；IR（KBr）ν：3417．2，2973．7，2935．1，1699．0，1454．1，1376．9，1317．1，1268．9，1166．7，1124．3，1076．1，1033．7，1018．2，1000．9 cm^{-1}；HRMS（FAB）m／z：計算値$C_{37}H_{63}NO_{13}Na$ $[M+Na]^+$ 752．4197，実測値752．4202

実施例8

デ（3'－N－メチル）－3'－N－スルフォニル－8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM727）の合成



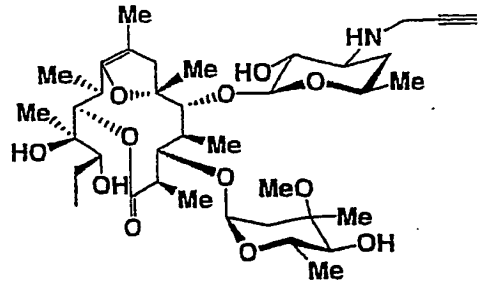
EM727

EM703（87.6mg，0.125mmol）のジクロロメタン（4.2mL）溶液に、0℃下、塩化メタンスルフォニル（9.3μL，0.249mmol）を加え、3時間攪拌した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール＝100：1→20：1］して、標記化合物EM727（37.2mg、収率91%、白色粉末）を得た。

EM727：m.p.：225－228℃；IR（KBr）ν：3497.6，2973.7，2935.1，1704.8，1463.7，1380.8，1326.8，1319.1，1265.1，1166.7，1141.7，1074.2，1041.4，1016.3cm^{-1}；HRMS（FAB）m／z：計算値$C_{37}H_{65}NO_{14}SNa$ $[M+Na]^+$ 802.4023，実測値802.3995

実施例9

ビス－デ（3'－N－メチル）－3'－N－プロパルギル－8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM728）の合成



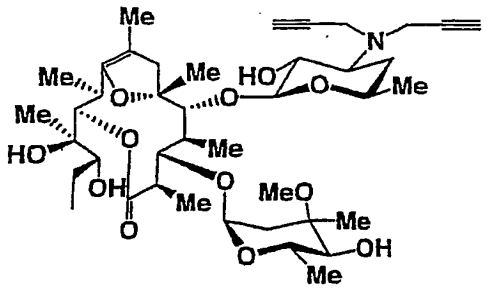
EM728

EM721（106．3mg，0．155mmol）とN，N－ジイソプロピルエチルアミン（269．3μL，1．546mmol）のジクロロメタン（5．2mL）溶液に3－ブロモプロピン（137．8μL，1．546mmol）を加え、室温で24時間攪拌した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝10：0．5：0．01→10：1：0．05］して、標記化合物EM728（41．3mg、収率37%、白色粉末）を得た。

EM728：m．p．：113－115℃；IR（KBr）ν：3413．0，2973．7，2935．1，1706．8，1457．9，1382．7，1263．1，1166．7，1126．2，1078．0，1039．4，1016．5 cm^{-1}；HRMS（FAB）m／z：計算値$C_{38}H_{63}NO_{12}Na$ $[M+Na]^+$ 748．4248，実測値748．4260

実施例10

ビス－デ（3'－N－メチル）－3'，3'－N，N－ジプロパルギル－8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM729）の合成



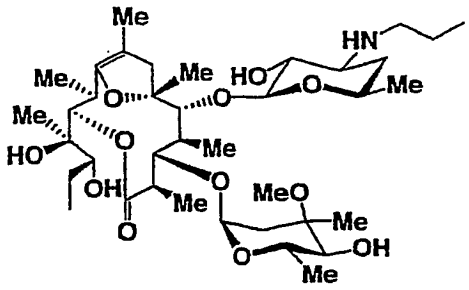
EM729

EM721（106．3mg，0．155mmol）とN，N－ジイソプロピルエチルアミン（269．3μL，1．546mmol）のジクロロメタン（5．2mL）溶液に3－ブロモプロピン（137．8μL，1．546mmol）を加え、室温で24時間撹拌した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝10：0．5：0．01→10：1：0．05］して、標記化合物EM729（27．9mg、収率24％、白色粉末）を得た。

EM729：m．p．：123－125℃；IR（KBr）ν：3415．0，3309．2，2971．8，2933．2，2877．3，1706．7，1457．9，1375．0，1263．1，1166．7，1116．6，1072．2，1049．1，1035．6，1016．3cm^{-1}；HRMS（FAB）m／z：計算値$C_{41}H_{65}NO_{12}Na$ $[M+Na]^+$ 786．4404，実測値786．4404

実施例11

ビス－デ（3'－N－メチル）－3'－N－プロピル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール（EM730）の合成



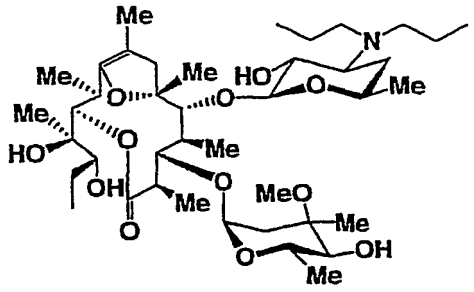
EM730

EM721（23．5mg，0．0342mmol）とアセトニトリル（2．3mL）溶液に、N，N－ジイソプロピルエチルアミン（59．6μL，0．342mmol）と1－ヨードプロパン（33．3μL，0．342mmol）を順次加え、80℃で20時間還流した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝15：1：0．1］して、標記の化合物EM730（5．7mg、収率23%、白色粉末）を得た。

EM730：m．p．：109－111℃；IR（KBr）ν：3435．0，2971．8，2935．1，2879．2，1706．7，1459．8，1380．8，1263．1，1166．7，1126．2，1078．0，1035．6，1016．3cm^{-1}；HRMS（FAB）m／z：計算値$C_{38}H_{67}NO_{12}Na$ $[M+Na]^+$ 752．4560，実測値752．4564

実施例12

ビス－デ（3'－N－メチル）－3'，3'－N，N－ジプロピル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール（EM731）の合成



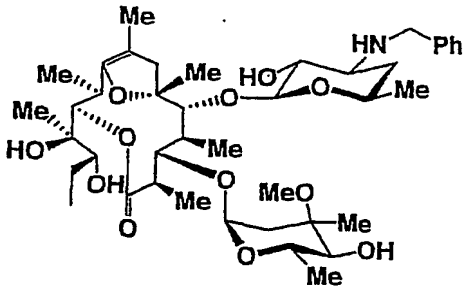
EM731

ＥＭ７２１（２３．５ｍｇ，０．０３４２ｍｍｏｌ）とアセトニトリル（２．３ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（５９．６μＬ，０．３４２ｍｍｏｌ）と１－ヨードプロパン（３３．３μＬ，０．３４２ｍｍｏｌ）を順次加え、８０℃で２０時間還流した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記化合物ＥＭ７３１（１２．０ｍｇ、収率４０％、白色粉末）を得た。

ＥＭ７３１：ｍ．ｐ．：１４８－１５１℃；ＩＲ（ＫＢｒ）ν：３４３５．０，２９６４．１，２９３３．２，２８７３．４，１７０６．７，１４５７．９，１３７６．９，１３１９．１，１２６３．１，１１６６．７，１１１０．８，１０８１．９，１０４９．１，１０３５．６，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{41}H_{73}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$７９４．５０３０，実測値７９４．５００５

実施例１３

ビス－デ（３’－Ｎ－メチル）－３’－Ｎ－ベンジル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７３２）の合成



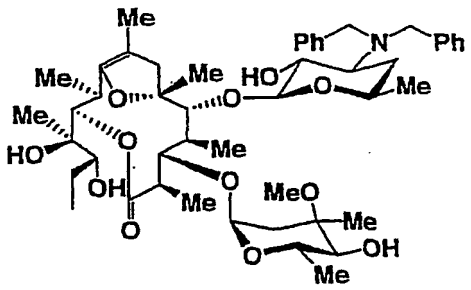
EM732

ＥＭ７２１（８８．８ｍｇ，０．１２９ｍｍｏｌ）とＮ，Ｎ－ジイソロピルエチルアミン（４５０．１μＬ，２．５８４ｍｍｏｌ）のジクロロメタン（４．３ｍＬ）溶液にベンジルクロライド（２９７．３μＬ，２．５８４ｍｍｏｌ）を室温で加え、９６時間攪拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記化合物ＥＭ７３２（４９．９ｍｇ、収率５０％、白色粉末）を得た。

ＥＭ７３２：ｍ．ｐ．：１２６－１２８℃；ＩＲ（ＫＢｒ）ν：３４１０．０，２９７１．８，２９３５．１，１７０６．７，１４５６．０，１３７８．９，１２６３．１，１１６６．７，１１２４．３，１０７８．０，１０４９．１，１０３９．４，１０１６．３，９８３．５，９３７．２，８０８．０，７５２．１ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{42}H_{67}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$８００．４５６０，実測値８００．４５６５

実施例１４

ビス－デ（3’－Ｎ－メチル）－3’，3’－Ｎ，Ｎ－ジベンジル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７３３）の合成



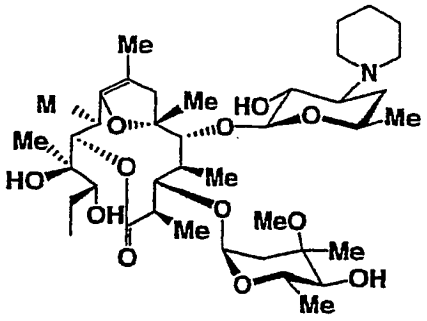
EM733

ＥＭ７２１（２６．８ｍｇ，０．０３９０ｍｍｏｌ）とアセトニトリル（１．３ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（１３５．９μＬ，０．７８０ｍｍｏｌ）とベンジルクロライド（８９．７μＬ，０．７８０ｍｍｏｌ）を順次加え、８０℃で６０時間還流した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記化合物ＥＭ７３３（１９．６ｍｇ、収率５８％、白色粉末）を得た。

ＥＭ７３３：ｍ．ｐ．：１４９－１５２℃；ＩＲ（ＫＢｒ）ν：３４２０．６，２９６９．８，２９３５．１，１７００．９，１４５４．１，１３７５．０，１３２４．９，１２６３．１，１１６６．７，１１１６．６，１０７６．１，１０４９．１，１０１６．３，７５２．１，７００．０ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{49}H_{73}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$８９０．５０３０，実測値８９０．５０３２

実施例１５

デ（３’－ジメチルアミノ）－３’－ピペリジノ－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７３４）の合成



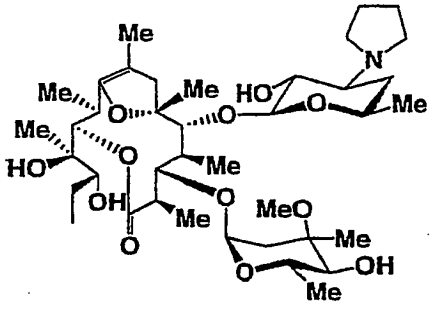
EM734

EM721（16．8mg，0．0244mmol）のアセトニトリル（4．9mL）溶液に、N，N－ジイソプロピルエチルアミン（42．5μL，0．244mmol）と1，5－ジブロモペンタン（33．2μL，0．244mmol）を順次加え、80℃で24時間還流した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝15：1：0．1］して、標記化合物EM734（13．3mg、収率72%、白色粉末）を得た。

EM734：m．p．：128－130℃；IR（KBr）ν：3420．0，2971．8，2935．1，2858．0，1710．6，1454．1，1380．8，1319．1，1263．1，1164．8，1110．8，1074．2，1047．2，1016．3 cm^{-1}；HRMS（FAB）m／z：計算値$C_{40}H_{70}NO_{12}$［M+Na］$^+$ 756．4897，実測値756．4901

実施例16

デ（3'－ジメチルアミノ）－3'－ピロリジノ－8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM735）の合成



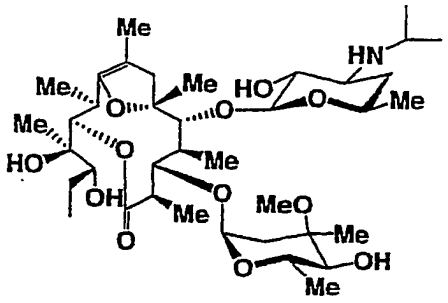
EM735

EM721（15．9mg，0．0231mmol）のアセトニトリル（4．6mL）溶液に、N，N－ジイソプロピルエチルアミン（40．2μL，0．231mmol）と1，4－ジブロモブタン（27．6μL，0．231mmol）を順次加え、80℃で24時間還流した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝10：1：0．1］して、標記化合物EM735（11．9mg、収率70%、白色粉末）を得た。

EM735：m．p．：127－129℃；IR（KBr）ν：3420．0，2971．8，2937．1，1702．8，1457．9，1382．7，1265．1，1166．7，1124．3，1076．1，1049．1，1016．3 cm^{-1}；HRMS（FAB）m／z：計算値$C_{39}H_{68}NO_{12}$［M+Na］$^+$ 742．4741，実測値742．4743

実施例17

ビス－デ（3'－N－メチル）－3'－N－（2－プロピル）－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール（EM736）の合成



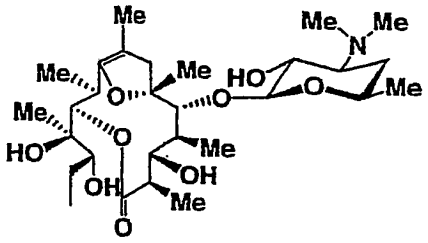
EM736

ＥＭ７２１（９０．６ｍｇ，０．１３２ｍｍｏｌ）のアセトニトリル（４．４ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（４５９．２μＬ，２．６３６ｍｍｏｌ）と２－ブロモプロパン（２４７．５μＬ，２．６３６ｍｍｏｌ）を順次加え、６０℃で７２時間攪拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：１：０．１］して、標記化合物ＥＭ７３６（２５．３ｍｇ、収率２６％、白色粉末）を得た。そして原料のＥＭ７２１を４７．１ｍｇ回収した（収率５２％）

ＥＭ７３６：ｍ．ｐ．：１０２－１０４℃；ＩＲ（ＫＢｒ）ν：３４２０．０，２９７１．８，２９３３．２，２８７７．３，１７１８．３，１４５９．８，１３８０．８，１２６３．１，１１６６．７，１１２６．２，１０７８．０，１０４９．１，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{38}H_{67}NO_{12}Na$［Ｍ＋Ｎａ］$^{+}$７５２．４５６０，実測値７５２．４５７６

実施例１８

デ（３－Ｏ－クラジノシル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７３７）の合成



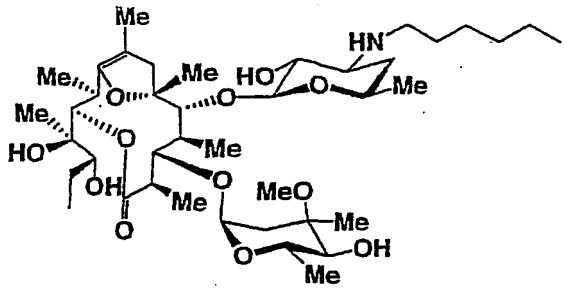
EM737

ＥＭ７０１（２０１．６ｍｇ，０．２８２ｍｍｏｌ）のジメチルホルムアミド（５．６ｍＬ）溶液に、ｐ－トルエンスルホン酸・一水和物（８０．３ｍｇ，０．４２２ｍｍｏｌ）を加え、５０℃で８時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、飽和炭酸水素ナトリウム水溶液でｐＨを８．０に調節した後、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記化合物ＥＭ７３７（８４．７ｍｇ、収率５４％、白色粉末）を得た。

ＥＭ７３７：ｍ．ｐ．：１０９－１１１℃；ＩＲ（ＫＢｒ）ν：３４８６．７，２９７３．７，２９３７．１，２８７７．３，１７０８．６，１６３１．５，１４５７．９，１３８２．７，１２６５．１，１１６４．８，１１１０．８，１０７６．１，１０３９．４ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{29}H_{52}NO_9$［Ｍ＋Ｈ］$^+$５５８．３６４１，実測値５５８．３６１６

実施例１９

ビス－デ（３’－Ｎ－メチル）－３’－Ｎ－ヘキシル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７３８）の合成



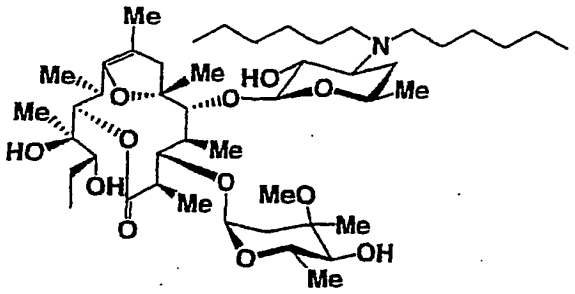
EM738

ＥＭ７２１（８０．６ｍｇ，０．１１７ｍｍｏｌ）のアセトニトリル（３．９ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（４０８．５μＬ，２．３４５ｍｍｏｌ）と１－ブロモヘキサン（３２８．７μＬ，２．３４５ｍｍｏｌ）を順次加え、６０℃で２４時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記化合物ＥＭ７３８（３３．７ｍｇ、収率４５％、白色粉末）を得た。そして原料のＥＭ７２１を２４．６ｍｇ回収した（収率３１％）

ＥＭ７３８：ｍ．ｐ．：１１５－１１８℃；ＩＲ（ＫＢｒ）ν：３４３０．３，２９６９．８，２９３３．２，２８５８．０，１７１２．５，１４５９．８，１３７８．９，１３１７．１，１２６３．１，１１６６．７，１１２６．２，１０７８．０，１０４７．２，１０３９．４，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{41}H_{74}NO_{12}$［Ｍ＋Ｈ］$^{+}$ ７７２．５２１０，実測値７７２．５２１４

実施例２０

ビス－デ（３’－Ｎ－メチル）－３’，３’－Ｎ，Ｎ－ジヘキシル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７３９）の合成



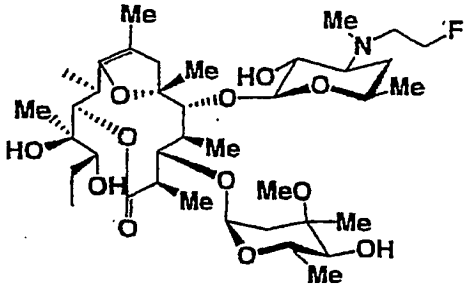
EM739

ＥＭ７２１（２２．９ｍｇ，０．０３３３ｍｍｏｌ）のアセトニトリル（１．１ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（１１６．０μＬ，０．６６６ｍｍｏｌ）と１－ブロモペキサン（９３．６μＬ，０．６６６ｍｍｏｌ）を順次加え、６０℃で７２時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記化合物ＥＭ７３９（２０．１ｍｇ、収率７１％、白色粉末）を得た。

ＥＭ７３９：ｍ．ｐ．：１５８－１６０℃；ＩＲ（ＫＢｒ）ν：３４９０．０，２９５８．３，２９３１．３，２８７１．５，２８５８．０，１７０２．８，１４５９．８，１３７６．９，１３１９．１，１２６５．１，１１６６．７，１１２６．２，１０８３．８，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：$C_{47}H_{86}NO_{12}$ ［Ｍ＋Ｈ］$^{+}$ 計算値８５６．６１４９，実測値８５６．６１３２

実施例２１

デ（３’－Ｎ－メチル）－３’－Ｎ－（２－フルオロエチル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７４０）の合成



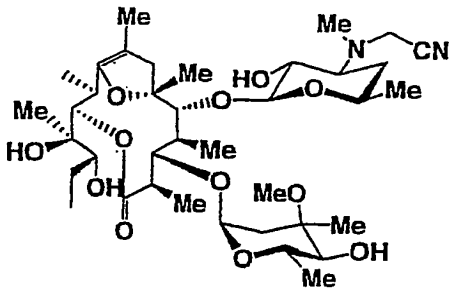
EM740

ＥＭ７０３（７０．０ｍｇ，０．０９９８ｍｍｏｌ）のジメチルホルムアミド（３．３ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（３４７．７μＬ，１．９９６ｍｍｏｌ）と１－ブロモ－2-フルオロエタン（１４８．６μＬ，１．９９６ｍｍｏｌ）を室温で加え、４８時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記化合物ＥＭ７４０（３６．０ｍｇ、収率４８％、白色粉末）を得た。そして、原料のＥＭ７０３を２５．５ｍｇ回収した（収率３６％）。

ＥＭ７４０：ｍ．ｐ．：１３８－１４０℃；ＩＲ（ＫＢｒ）ν：３４８０．８，２９７３．７，２９３７．１，２８７９．２，１７０４．８，１４５７．９，１３７６．９，１３１９．１，１２６５．１，１１６６．７，１１２６．２，１１１４．７，１０７６．１，１０４９．１，１０３５．６，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{38}H_{66}NO_{12}FNa$［Ｍ＋Ｎａ］$^{+}$７７０．４４６７，実測値７７０．４４６９

実施例２２

デ（3’－Ｎ－メチル）－3’－シアノメチル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７４２）の合成



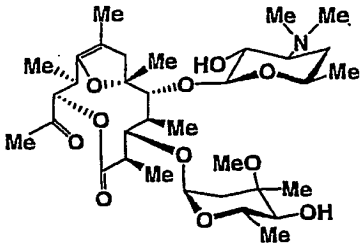
EM742

ＥＭ７０３（６４．６ｍｇ，０．０９２１ｍｍｏｌ）のジメチルホルムアミド（３．１ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（３２０．９μＬ，１．８４７ｍｍｏｌ）とブロモアセトニトリル（１２８．３μＬ，１．８４７ｍｍｏｌ）を室温で加え、４時間攪拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフイーで精製［クロロルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記化合物ＥＭ７４２（５３．１ｍｇ、収率７８％、白色粉末）を得た。

ＥＭ７４２：ｍ．ｐ．：１１０－１１２℃；ＩＲ（ＫＢｒ）ν：３４８５．５，２９７３．７，２９３５．１，２８６３．８，１７０２．８，１４５６．０，１３８２．７，１３１９．１，１２６５．１，１１６６．７，１１２６．２，１０７４．２，１０３７．５，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）：計算値$C_{38}H_{64}N_2O_{12}Na$［Ｍ＋Ｎａ］$^+$ ７６３．４３５６，実測値７６３．４３７７

参考例２

デ（１２－ヒドロキシ）－デ［１２－（１－ヒドロキシプロピル）］－１２－オキソ－８，９－無水－シュードエリスロマイシンＡ６，９－ヘミケタール（ＥＭ７０５）の合成



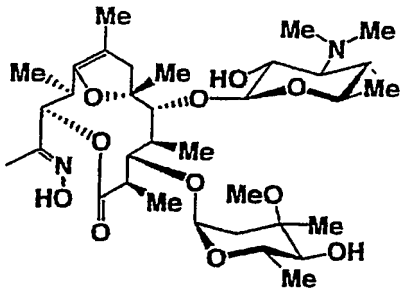
EM 705

ＥＭ７０１（５０８．０ｍｇ，０．７０１ｍｍｏｌ）のジクロロメタン（２４．０ｍｌ）溶液に、四酢酸鉛（５０８．０ｍｇ，１．１３６ｍｍｏｌ）を加え、室温で４０分撹拌した。ＴＬＣで反応終了を確認した後、反応液は飽和食塩水－飽和炭酸水素ナトリウム水溶液（１：１ｖ／ｖ）で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール、アンモニア水溶液＝１０：０．５：０．０１］して、標記化合物ＥＭ７０５（２８２．７ｍｇ、収率６１％、白色粉末）を得た。

ＥＭ７０５：ｍ．ｐ．：１０８－１１２℃；ＩＲ（ＫＢｒ）ν：３４８８，２９７２，２９３７，２８８３，１７４０，１７２４，１４５８，１３７９，１２４４，１１６５，１１０７，１０９３，１０７６，１０５５，１０３４，１０１６ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）：計算値$C_{34}H_{58}NO_{11}$［Ｍ＋Ｈ］$^{+}$６５６．４０１０，実測値６５６．４０２１

実施例２３

デ（１２－ヒドロキシ）－デ［１２－（１－ヒドロキシプロピル）］－１２－ヒドロキシオキシム－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩（ＥＭ７４３）の合成



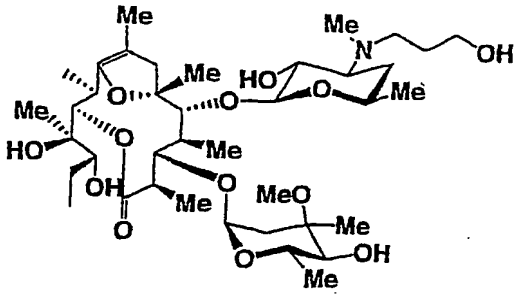
EM743

EM705（116.5mg，0.1781mmol）とヒドロキシルアミン塩酸塩（32.0mg，0.533mmol）を加えたエタノール（0.9mL）溶液に、ピリジン（0.9mL）を0℃下ゆっくり加え、3時間攪拌した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフイーで精製［クロロルム：メタノール：アンモニア水溶液＝10：0.5：0.01→10：1：0.05］して、標記化合物EM743（114.5mg、収率96%、白色粉末）を得た。

EM743：m.p.：141－143℃；IR（KBr）ν：3485.8，2971.8，2937.1，2883.1，1737.5，1459.8，1378.9，1255.4，1247.7，1166.7，1112.7，1089.6，1076.1，1037.5，1014.4 cm^{-1}；HRMS（FAB）m／z：計算値$C_{34}H_{59}N_2O_{11}$ $[M+H]^+$ 671.4112，実測値671.4108

実施例24

デ（3'－N－メチル）－3'－N－3－ヒドロキシー1－プロピルー8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール（EM744）の合成



EM744

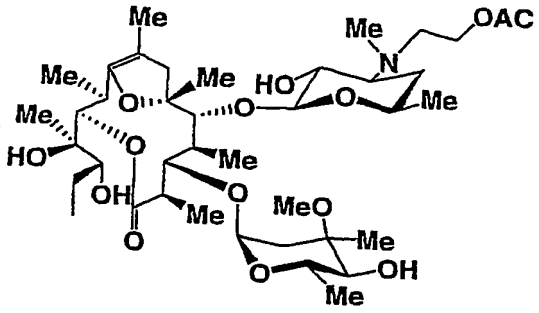
ＥＭ７０３（６８．１ｍｇ，０．０９７１ｍｍｏｌ）のジメチルホルムアミド（３．３ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（３３８．３μＬ，１．９４２ｍｍｏｌ）と３－ブロモ－１－プロパノール（１７５．６μＬ，１．９４２ｍｍｏｌ）を室温で加え、４８時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記の化合物ＥＭ７４４（２７．７ｍｇ、収率３８％、白色粉末）を得た。そして原料のＥＭ７０３を２２．５ｍｇ回収した（収率３３％）。

ＥＭ：７４４：ｍ．ｐ．：１４２－１４５℃；ＩＲ（ＫＢｒ）ν：３４７８．８，２９７３．７，２９３７．１，２８７７．３，１７００．９，１６３５．３，１４５９．８，１４０３．９，１３８２．７，１３１７．１，１２６７．０，１１６６．７，１１２６．２，１１１４．７，１０７６．１，１０４９．１，１０３５．６，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{39}H_{69}NO_{13}Na$［Ｍ＋Ｎａ］$^{+}$ ７８２．４６６６，実測値７８２．４６６７

実施例２５

デ（３’－Ｎ－メチル）－３’－Ｎ－（２－アセトキシエチル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７４５）の合

成



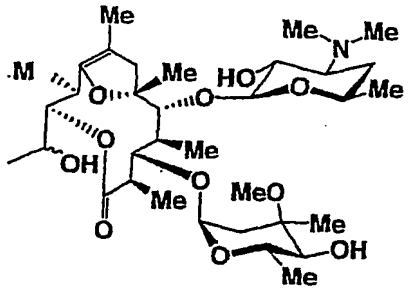
EM 745

ＥＭ７０３（２１．５ｍｇ，０．０３０７ｍｍｏｌ）のジメチルホルムアミド（１．０ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（１０６．８μＬ，０．６１３ｍｍｏｌ）と２－ブロモエチルアセテート（６７．６μＬ，０．６１３ｍｍｏｌ）を室温で加え、４８時間攪拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記の化合物ＥＭ７４５（６．０ｍｇ、収率２５％、白色粉末）を得た。

ＥＭ：７４５：ｍ．ｐ．：１３１－１３３℃；ＩＲ（ＫＢｒ）ν：３５００．２，３４７７．０，２９７３．７，２９３７．１，２８７７．３，１７３５．６，１７００．９，１４５７．９，１３７６．９，１３１９．１，１２６５．１，１１６６．７，１１２６．２，１０７８．０，１０３７．５，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{40}H_{69}NO_{14}Na$［Ｍ＋Ｎａ］８１０．４６１５，実測値８１０．４６２９

実施例２６

デ［１２－（ヒドロキシプロピル）］－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７４６）の合成



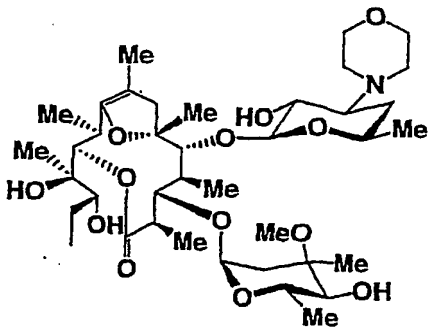
EM746

－７８℃下、ＥＭ７０５（３７．７ｍｇ，０．０５７５ｍｍｏｌ）のメタノール（２．９ｍＬ）溶液に、水酸化ほう素ナトリウム（２１．８ｍｇ，０．５７５ｍｍｏｌ）を加え、３０分間攪拌した。次いで０℃に昇温し、更に３０分攪拌した。ＴＬＣで反応終了を確認した後、アセトン（０．５ｍＬ）を加えて反応を停止し、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフイーで精製［クロロルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記化合物ＥＭ７４６（３５．８ｍｇ、収率９５％、白色粉末）を得た。

ＥＭ：７４６：m．ｐ．：１１６－１１８℃；ＩＲ（ＫＢｒ）ν：３４５７．７，２９７１．３，２９３９．０，１７３１．８，１６３１．５，１４５７．９，１３７８．９，１２６５．１，１１６６．７，１１１０．８，１０７８．０，１０４１．４，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{34}H_{59}NO_{11}Na$［Ｍ＋Ｎａ］$^{+}$ ６８０．３９６３，実測値６８０．３９６３

実施例２７

デ（3’－ジメチルアミノ）－3’－モルホリノ－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７４７）の合成



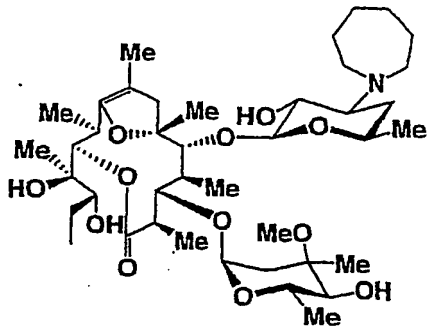
EM747

EM721（18．1mg，0．0263mmol）のアセトニトリル（2．6mL）溶液に、N，N－ジイソプロピルエチルアミン（45．8μL，0．263mmol）とビス（2－ブロモエチル）エーテル（33．1μL，0．263mmol）を順次加え、80℃で24時間攪拌した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタン出抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝20：1：0．1］して、標記化合物EM747（12．0mg、収率60%、白色粉末）を得た。

EM：747：m．p．：139－142℃；IR（KBr）ν：3452．0，2971．8，2937．1，2865．7，1700．9，1646．9，1457．9，1380．8，1319．1，1265．1，1166．7，1110．8，1072．2，1049．1，1016．3 cm^{-1}；HRMS（FAB）m／z：計算値$C_{39}H_{67}NO_{13}Na$［M+Na］$^+$ 780．4510，実測値780．4529

実施例28

デ（3'－ジメチルアミノ）－3'－［ヘキサヒドロ－1（1H）－アゼピニル］－8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM748）の合成



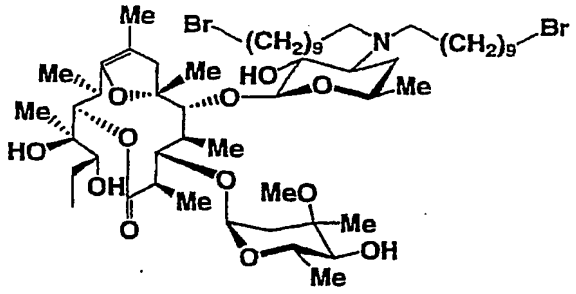
EM748

EM721（19．5mg，0．0284mmol）のアセトニトリル（2．8mL）溶液に、N，N－ジイソプロピルエチルアミン（49．5μL，0．284mmol）と1，6－ジブロモヘキサン（43．6μL，0．284mmol）を順次加え、80℃で24時間還流した。TLCで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝20：1：0．1］して、標記化合物EM748（11．7mg、収率54%、白色粉末）を得た。

EM748：m．p．：120－123℃；IR（KBr）ν：3430．7，2971．8，2933．2，2858．0，1708．6，1629．6，1457．9，1378．9，1319．1，1263．1，1166．7，1112．7，1083．8，1047．2，1016．3 cm^{-1}；HRMS（FAB）m／z：$C_{41}H_{72}NO_{12}$ $[M+H]^+$ 770．5054，実測値770．5062

実施例29

ビス－デ（3'－N－メチル）－3'，3'－N，N－ジ（10－ブロモ－1－デカニル）－8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM749）の合成



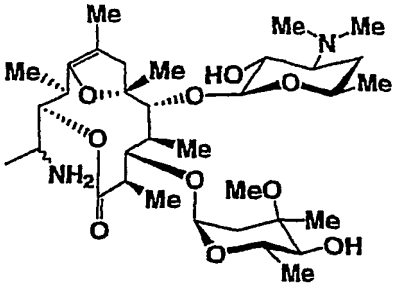
EM749

ＥＭ７２１（１８．０ｍｇ，０．０２６２ｍｍｏｌ）のアセトニトリル（２．６ｍＬ）溶液に、Ｎ，Ｎ－ジイソプロピルエチルアミン（４５．６μＬ，０．２６２ｍｍｏｌ）と１，１０－ジブロモデカン（５８．９μＬ，０．２６２ｍｍｏｌ）を順次加え、８０℃で３６時間還流した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝２０：１：０．１］して、標記化合物ＥＭ７４９（１４．９ｍｇ、収率５１％、白色粉末）を得た。

ＥＭ７４９：ｍ．ｐ．：１３２－１３４℃；ＩＲ（ＫＢｒ）ν：３４４８．１，２９２９．３，１７００．９，１６２９．６，１４５９．８，１３７５．０，１３１９．１，１２６７．０，１１６６．７，１１２６．２，１０８１．９，１０４９．１，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{55}H_{100}NO_{12}Br_2$［Ｍ＋Ｈ］$^+$ １１２６，実測値１１２６

実施例３０

デ（１２－ヒドロキシ）－デ［１２－（ヒドロキシプロピル）］－１２－アミノ－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７５０）の合成



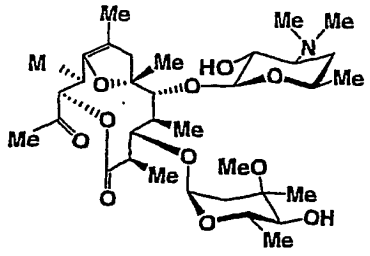
EM750

EM743（15．5mg，0．0231mmol）のエタノール（2．3mL）溶液に、酸化モリブデン（IV）（10．0mg，0．0694mmol）と水酸化ほう素ナトリウム（10．5mg，0．277mmol）を0℃下加え、4時間撹拌した。TLCで反応終了を確認した後、アセトン（0．5mL）を加え反応を停止し、反応液は飽和食塩水ー飽和炭酸水素ナトリウム水溶液（1：1v／v）で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝10：1：0．1］して、標記化合物EM750（13．4mg、収率88%、白色粉末）を得た。

EM750：m．p．：104－107℃；IR（KBr）ν：3448．1，2971．8，2935．1，1729．8，1629．6，1457．9，1378．9，1259．3，1166．7，1114．7，1078．0，1039．4，1016．3cm^{-1}；HRMS（FAB）m／z：計算値$C_{34}H_{60}N_2O_{10}Na$ $[M+Na]^+$ 679．4145，実測値679．4117

参考例3

デ（3'－N－メチル）－デ（12－ヒドロキシ）－デー［12－（1－ヒドロキシプロピル）］－12－オキソー8，9－無水－シュードエリスロマイシンA 6，9－ヘミケタール（EM706）の合成



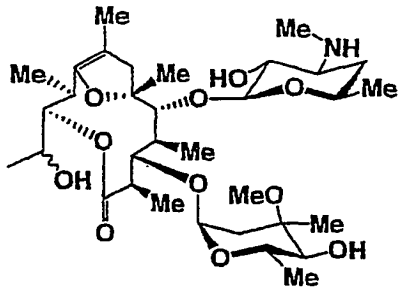
EM 706

EM７０１（５０８．０ｍｇ，０．７０１ｍｍｏｌ）のジクロロメタン（２４．０ｍｌ）溶液に、四酢酸鉛（５０８．０ｍｇ，１．１３６ｍｍｏｌ）を加え、室温で４０分撹拌した。ＴＬＣで反応終了を確認した後、反応液は飽和食塩水－飽和炭酸水素ナトリウム水溶液（１：１ｖ／ｖ）で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝１０：０．５：０．０１］して、標記化合物ＥＭ７０６（７１．６ｍｇ、収率１６％、白色粉末）を得た。

ＥＭ７０６：ｍ．ｐ．：１７６－１７９℃；ＩＲ（ＫＢｒ）ν：３４６８，２９６６，２９２６，２８５２，．２３６０，１７３６，１７１８，１５５８，１４６２，１３７９，１２４６，１１６５，１１２６，１０９９，１０７６，１０３８，１０１６ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）：計算値$C_{33}H_{56}NO_{11}$［Ｍ＋Ｈ］$^{+}$ ６４２．３８５３，実測値６４２．３８６６

実施例３１

デ（3’－Ｎ－メチル）－デ［１２－（１－ヒドロキシプロピル）］－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７５１）の合成



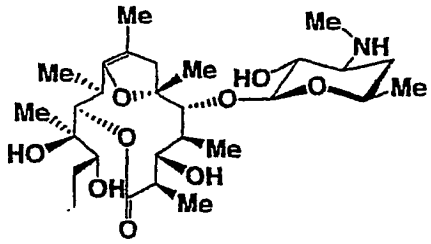
EM751

ＥＭ７０６（３８．８ｍｇ，０．０６０５ｍｍｏｌ）のメタノール（３．０ｍＬ）溶液に、水酸化ほう素ナトリウム（２２．９ｍｇ，０．６０５ｍｍｏｌ）を０℃下加え、１時間撹拌した。ＴＬＣで反応終了を確認した後、アセトン（０．５ｍＬ）を加え反応を停止し、反応液は飽和食塩水ー飽和炭酸水素ナトリウム水溶液（１：１，ｖ／ｖ）で希釈し、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフイーで精製［クロロホルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記化合物ＥＭ７５１（３１．４ｍｇ、収率８１％、白色粉末）を得た。

ＥＭ７５１：ｍ．ｐ．：１２３－１２５℃；ＩＲ（ＫＢｒ）ν：３５０４．０，３４４８．１，２９７１．８，２９３５．１，１７２９．８，１６６４．３，１５９４．８，１４５７．９，１３７８．９，１３４４．１，１２６５．１，１１６６．７，１１２６．２，１０７８．０，１０４１．４，１０１６．３ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{33}H_{58}NO_{11}$［Ｍ＋Ｈ］$^{+}$６４４．３９８７，実測値６４４．４０１１

実施例３２

デ（３－Ｏ－クラジノシル）－デ（３’－Ｎ－メチル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール（ＥＭ７５４）の合成



EM754

ＥＭ７０３（１３２．４ｍｇ，０．１８９ｍｍｏｌ）のジメチルホルムアミド（３．８ｍＬ）溶液に、ｐ－トルエンスルホン酸・一水和物（５３．９ｍｇ，０．２８３ｍｍｏｌ）を加え、５０℃で６時間撹拌した。ＴＬＣで反応終了を確認した後、反応液は水で希釈し、飽和炭酸水素ナトリウム水溶液でｐＨを８に調節した後、ジクロロメタンで抽出した。有機層を芒硝で脱水した後、芒硝をろ過し、溶媒を留去して粗物質を得た。この粗物質をシリカゲルカラムクロマトグラフィーで精製［クロロホルム：メタノール：アンモニア水溶液＝１５：１：０．１］して、標記の化合物ＥＭ７５４（５０．２ｍｇ、収率４９％、白色粉末）を得た。

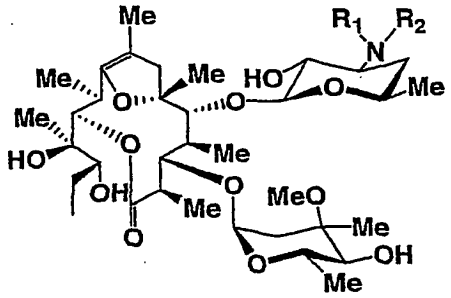
ＥＭ７５４：ｍ．ｐ．：２１８－２２１℃；ＩＲ（ＫＢｒ）ν：３４３２．７，２９６９．８，２９２７．４，２８５８．０，１７０８．６，１６２９．６，１４５７．９，１４０５．９，１３８０．８，１３１９．１，１２７０．９，１２３２．３，１１３０．１，１０７８．０，１０３９．４ｃｍ$^{-1}$；ＨＲＭＳ（ＦＡＢ）ｍ／ｚ：計算値$C_{28}H_{49}NO_9$ Ｎａ［Ｍ＋Ｎａ］$^+$ ５６６．３３０５，実測値５６６．３３１１

発明の効果

本発明の新規シュードエリスロマイシンは、減少した抗菌活性と、増加した抗炎症作用を有し、新たな抗炎症剤として期待される。

請 求 の 範 囲

1. 下記一般式［Ｉ］



［Ｉ］

式中、R_1 およびR_2 は、同じかまたは異なり、それぞれH，アルキル、アルキニル、アシル、スルホニルを示し、これらは置換基を有していてもよい、Ｍｅはメチルを示す、で表される新規シュードエリスロマイシン誘導体。

2. デ（3’－Ｎ－メチル）－8，9－無水－シュードエリスロマイシンＡ 6，9－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

3. デ（3’－Ｎ－メチル）－3’－Ｎ－スルフォニル－8，9－無水－シュードエリスロマイシンＡ 6，9－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

4. デ（3’－Ｎ－メチル）－［3’－Ｎ－（3－ヒドロキシ－1－プロピル）］－8，9－無水－シュードエリスロマイシンＡ 6，9－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

5. デ（3’－Ｎ－メチル）－3’－Ｎ－（2－アセトキシエチル）－8，9－無水－シュードエリスロマイシンＡ 6，9－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

6．　デ（3’－N－メチル）－3’－N－シアノメチル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

7．　デ（3’－N－メチル）－3’－N－（2－フルオロエチル）－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

8．　ビス－デ（3’－N－メチル）－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

9．　ビス－デ（3’－N－メチル）－3’－N－エチル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

10．　ビス－デ（3’－N－メチル）－3’，3’－N，N－ジエチル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

11．　ビス－デ（3’－N－メチル）－3’－N－アリル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

12．　ビス－デ（3’－N－メチル）－3’，3’－N，N－ジアリル－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲1記載の化合物。

１３．　ビス－デ（3’－Ｎ－メチル）－3’－Ｎ－プロパルギル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

１４．　ビス－デ（3’－Ｎ－メチル）－3’，3’－Ｎ，Ｎ－ジプロパルギル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

１５．　ビス－デ（3’－Ｎ－メチル）－3’－Ｎ－プロピル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

１６．　ビス－デ（3’－Ｎ－メチル）－3’，3’－Ｎ，Ｎ－ジプロピル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

１７．　ビス－デ（3’－Ｎ－メチル）－3’－Ｎ－ヘキシル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

１８．　ビス－デ（3’－Ｎ－メチル）－3’，3’－Ｎ，Ｎ－ジヘキシル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

１９．　ビス－デ（3’－Ｎ－メチル）－3’－Ｎ－ベンジル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

２０．　ビス－デ（３’－Ｎ－メチル）－３’，３’－Ｎ，Ｎ－ジベンジル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

２１．　ビス－デ（３’－Ｎ－メチル）－３’－Ｎ－（２－プロピル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

２２．　ビス－デ（３’－Ｎ－メチル）－３’，３’－Ｎ，Ｎ－ジ－（１０－ブロモ－１－デカニル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲１記載の化合物。

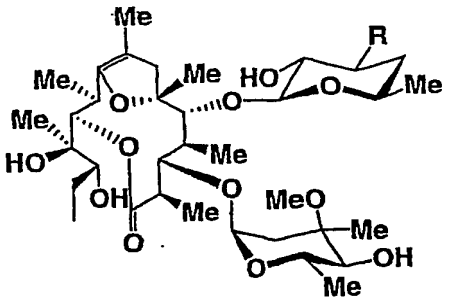
２３．　ビス－デ（３’－Ｎ－メチル）－３’－Ｎ－アセチル－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケターまたはその塩である請求の範囲１記載の化合物。

２４．　一般式［Ｉ］で表される化合物が、単球からマクロファージへの分化誘導促進作用を有する請求の範囲１記載の誘導体。

２５．　一般式［Ｉ］で表される化合物が、ブレオマイシン肺繊維症に対し抑制効果を有する請求の範囲１記載の誘導体。

２６．　一般式［Ｉ］で表される化合物が、インフルエンザウイルス感染による肺炎の抑制効果を有する請求の範囲１記載の誘導体。

２７．　下記一般式［II］



[II]

式中、Rは、Nを含むヘテロ環を示し、これらは置換基を有していてもよい、Meはメチルを示す、で表される新規シュードエリスロマイシン誘導体。

２８．　デ（3’－ジメチルアミノ）－3’－ピペリジノ－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲２７記載の化合物。

２９．　デ（3’－ジメチルアミノ）－3’－ピロリジノ－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲２７記載の化合物。

３０．　デ（3’－ジメチルアミノ）－3’－モルフォリノ－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタールまたはその塩である請求の範囲２７記載の化合物。

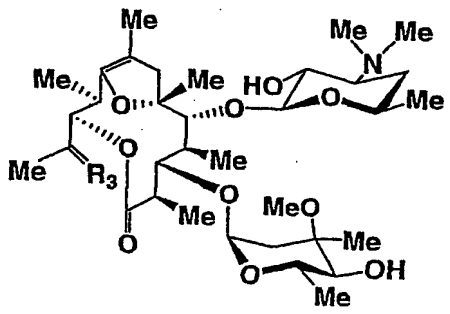
３１．　デ（3’－ジメチルアミノ）－3’－［ヘキサヒドロ－1（1H）－アゼピニル］－8，9－無水－シュードエリスロマイシンA　6，9－ヘミケタール、またはその塩である請求の範囲２７記載の化合物。

３２．　一般式［Ⅱ］で表される化合物が、単球からマクロファージへの分化誘導促進作用を有する請求の範囲２７記載の誘導体。

３３．　一般式［Ⅱ］で表される化合物が、ブレオマイシン肺繊維症に対し抑制効果を有する請求の範囲２７記載の誘導体。

３４．　一般式［Ⅱ］で表される化合物が、インフルエンザウイルス感染による肺炎の抑制効果を有する請求の範囲２７記載の誘導体。

３５．　下記一般式［Ⅲ］



［Ⅲ］

式中、R_3 はＯまたはＮＯＨ、Ｍｅはメチルを示す、で表される新規シュードエリスロマイシン誘導体。

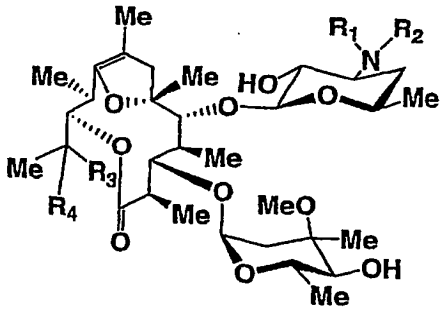
３６．　デ（１２－ヒドロキシ）－デ［１２－（１－ヒドロキシプロピル）］－１２－ヒドロキシオキシム－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲３５記載の化合物。

３７．　一般式［Ⅲ］で表される化合物が、単球からマクロファージへの分化誘導促進作用を有する請求の範囲３５記載の誘導体。

３８．　一般式［Ⅲ］で表される化合物が、ブレオマイシン肺繊維症に対し抑制効果を有する請求の範囲３５記載の誘導体。

３９．　一般式［Ⅲ］で表される化合物が、インフルエンザウイルス感染による肺炎の抑制効果を有する請求の範囲３５記載の誘導体。

４０．　下記一般式［Ⅳ］



［Ⅳ］

式中、R_1 およびR_2 は、同じかまたは異なり、それぞれH、メチルを示し、R_3 およびR_4 は、それぞれH、水酸基、アミノ基を示す、Ｍｅはメチル、で表される新規シュードエリスロマイシン誘導体。

４１．　デ［１２－（１－ヒドロキシプロピル）］－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲４０記載の化合物。

４２．　デ（１２－ヒドロキシ）－デ［１２－（１－ヒドロキシプロピル）］－１２－アミノ－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲４０記載の化合物。

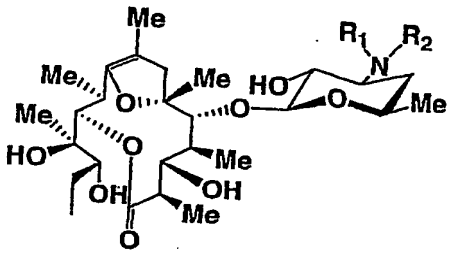
４３．　デ（３’－Ｎ－メチル）－デ［１２－（１－ヒドロキシプロピル）］－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲４０記載の化合物。

４４．　一般式［Ⅳ］で表される化合物が、単球からマクロファージへの分化誘導促進作用を有する請求の範囲４０記載の誘導体。

４５．　一般式［Ⅳ］で表される化合物が、ブレオマイシン肺繊維症に対し抑制効果を有する請求の範囲４０記載の誘導体。

４６．　一般式［Ⅳ］で表される化合物が、インフルエンザウイルス感染による肺炎の抑制効果を有する請求の範囲４０記載の誘導体。

４７．　下記一般式［Ｖ］



［Ｖ］

式中、R_1 およびR_2 は、同じかまたは異なり、それぞれH、メチルを示し、Meはメチルを示す、で表される新規シュードエリスロマイシン誘導体。

４８．　デ（３－Ｏ－クラジノシル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲４７記載の化合物。

４９．　デ（３－Ｏ－クラジノシル）－デ（３’－Ｎ－メチル）－８，９－無水－シュードエリスロマイシンＡ　６，９－ヘミケタール、またはその塩である請求の範囲４７記載の化合物。

５０．　一般式［Ｖ］で表される化合物が、単球からマクロファージへの分化誘導促進作用を有する請求の範囲４７記載の誘導体。

５１．　一般式［Ｖ］で表される化合物が、ブレオマイシン肺繊維症に対し抑制効果を有する請求の範囲４７記載の誘導体。

５２．　一般式［Ｖ］で表される化合物が、インフルエンザウイルス感染による肺炎の抑制効果を有する請求の範囲４７記載の誘導体。

FIG. 1

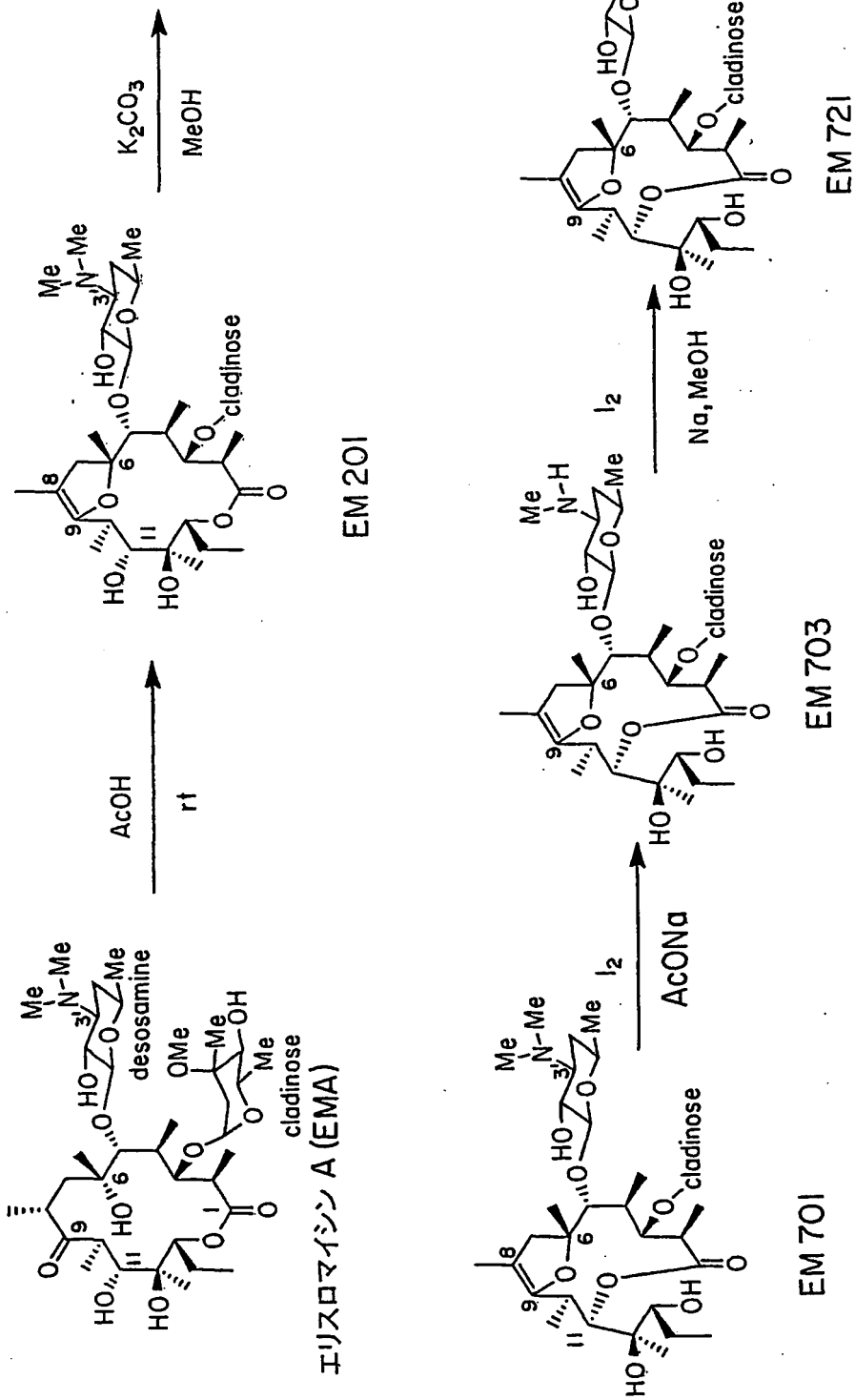

AcOH
rt
K_2CO_3
MeOH
AcONa
I_2
Na, MeOH
desosamine
cladinose
エリスロマイシン A (EMA)
EM 201
EM 701
EM 703
EM 721

FIG. 2

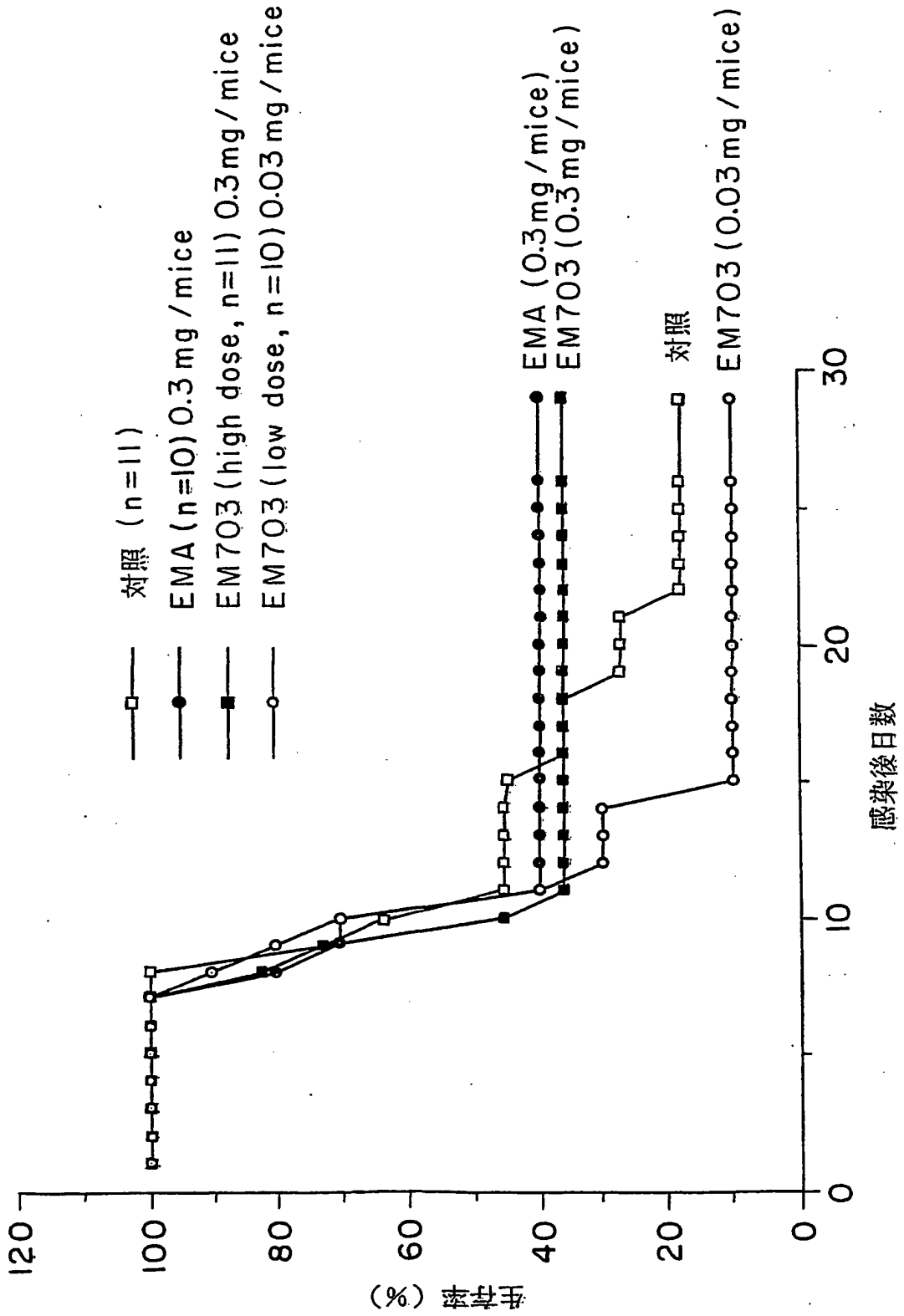
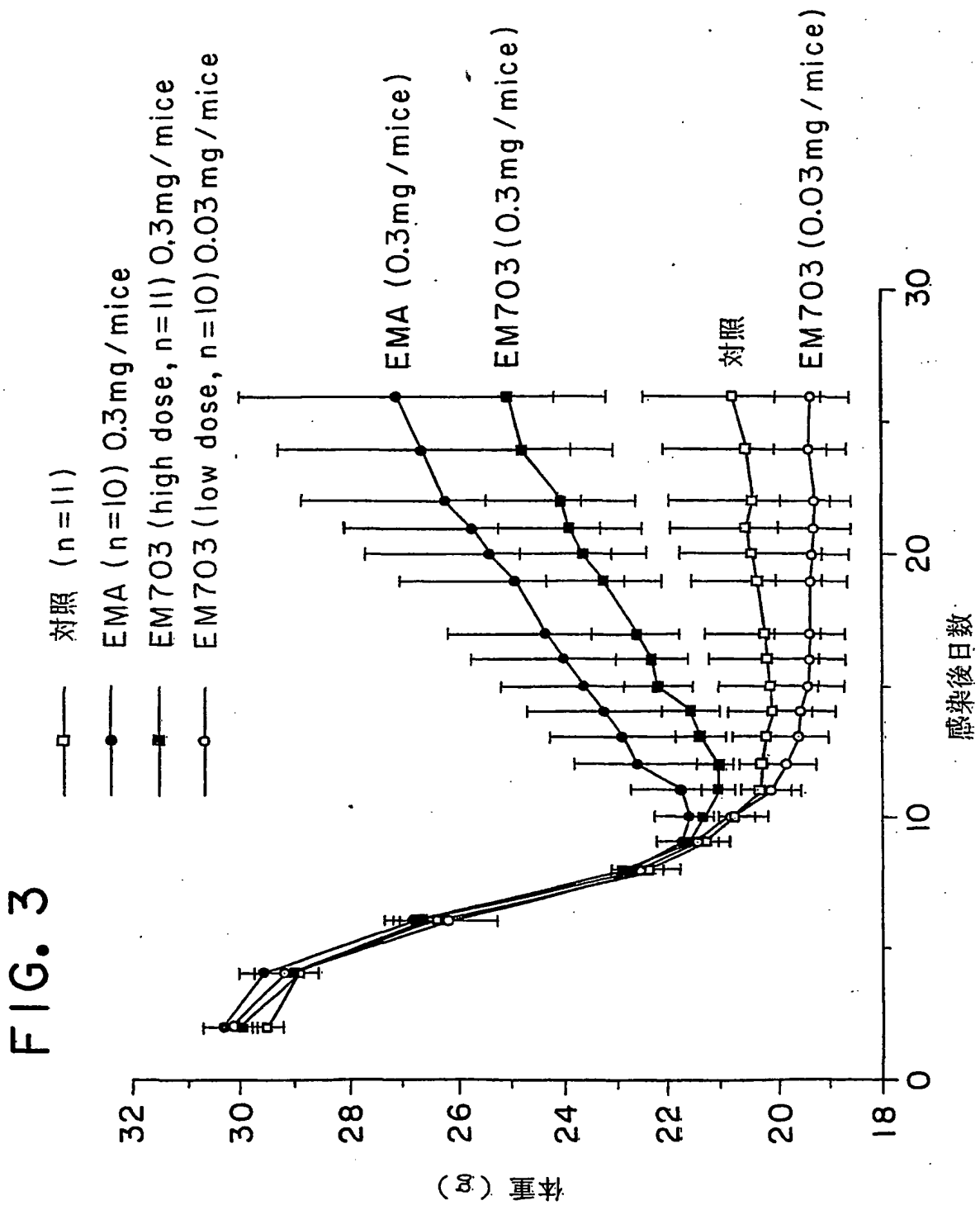

対照 (n=11)
EMA (n=10) 0.3 mg/mice
EM703 (high dose, n=11) 0.3mg/mice
EM703 (low dose, n=10) 0.03 mg/mice
EMA (0.3mg/mice)
EM703 (0.3mg/mice)
対照
EM703 (0.03mg/mice)
生存率 (%)
感染後日数
120
100
80
60
40
20
0
0
10
20
30

FIG. 3


対照 (n=11)
EMA (n=10) 0.3mg/mice
EM703 (high dose, n=11) 0.3mg/mice
EM703 (low dose, n=10) 0.03mg/mice
EMA (0.3mg/mice)
EM703 (0.3mg/mice)
対照
EM703 (0.03mg/mice)
体重 (g)
感染後日数
32
30
28
26
24
22
20
18
0
10
20
30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/05503

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07H17/08 // A61K31/7048, A61P11/00, 29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07H17/08 // A61K31/7048, A61P11/00, 29/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), MEDLINE (STN), EMBASE (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 838469 A (Solvay Pharmaceuticals GmbH), 29 April, 1998 (29.04.98) & DE 19644195 A & US 5912235 A & JP 10-130297 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 128:308701 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1,2,21,24-26 1-52
X Y	EP 550895 A1 (Kali-Chemie Pharma GmbH), 14 July, 1993 (14.07.93) & DE 4200145 A & US 5418224 A & JP 7-247299 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 119:271625 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1,2,21,24-26 1-52

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October, 2000 (24.10.00)	07 November, 2000 (07.11.00)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP00/05503

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 382472 A2 (Lilly, Eli, and Co.), 16 August, 1990 (16.08.90) & US 5106961 A & JP 2-240095 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 114:102696 especially, compounds of RN:132201-81-1, 121590-61-2, 132137-36-1	35,37-39 1-52
X Y	EP 296717 A2 (Lilly, Eli, and Co.), 28 December, 1988 (28.12.88) & JP, 63-307894, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 111:58271 especially, compounds of RN:105882-69-7, 105882-72-2 121590-61-2	1,24-26,35, 37-39 1-52
X Y	KIBWAGE I.O., et al, "Identification of novel erythromycin derivatives in mother liquor concentrates of Streptomyces erythraeus", J. Antibiot, (1987), Vol.40, No.1, pages 1 to 6 & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 106:172535 especially, compounds of RN:107745-55-1, 105882-69-7	1,24-26 1-52
X Y	EP 937734 A1 (Solvay Pharmaceuticals G.m.b.H.), 25 August, 1999 (25.08.99) & DE 19805822 A & JP 11-269193 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 131:144790 especially, compounds of RN:236099-91-5,151052-42-5	1,24-26 1-52
X Y	WO 92/18134 A1 (Abbott Laboratories), 29 October, 1992 (29.10.92) & EP 579770 A1 & JP 6-509326 A & US 5538961 A & US 5523418 A & US 5523401 A & US 5554605 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 118:101716 especially, compounds of RN:105882-69-7, 145692-88-2, 145692-89-3, 145692-94-0, 145692-95-1, 145692-97-3, 145693-00-1, 145693-01-2, 145693-02-3, 145693-03-4, 145774-00-1	1,24-26 1-52
X Y	EP 349100 A2 (Lilly, Eli, and Co.) 03 January, 1990 (03.01.90) & US 4920102 A & JP 1-311096 A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 113:59777 especially, compounds of RN:105882-69-7, 127931-39-9, 127966-89-6	1,24-26 1-52

国際調査報告

国際出願番号 PCT／JP00／05503

A. 発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl' C07H17/08 // A61K31/7048, A61P11/00, 29/00

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl' C07H17/08 // A61K31/7048, A61P11/00, 29/00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS (STN), MEDLINE (STN), , EMBASE (STN)

C. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X / Y	EP, 838469, A (Solvay Pharmaceuticals G.m.b.H.) 29.4月.1998 (29.04.98) & DE, 19644195, A & US, 5912235, A & JP, 10-130297, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.128:308701 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1, 2, 21, 24-26 / 1-52

☒ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊ 引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
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「Y」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日　24.10.00	国際調査報告の発送日　07.11.00
国際調査機関の名称及びあて先 日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特許庁審査官（権限のある職員）　４Ｃ　９４５５ 森井　隆信 電話番号　０３－３５８１－１１０１　内線　３４５１

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（１９９８年７月）

C（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X / Y	EP, 550895, A1 (Kali-Chemie Pharma GmbH) 14.7月.1993(14.07.93) & DE, 4200145, A & US, 5418224, A & JP, 7-247299, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.119:271625 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1, 2, 21, 24-26 / 1-52
X / Y	EP, 382472, A2 (Lilly, Eli, and Co.) 16.8月.1990(16.08.90) & US, 5106961, A & JP, 2-240095, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.114:102696 especially, compounds of RN:132201-81-1, 121590-61-2, 132137-36-1	35, 37-39 / 1-52
X / Y	EP, 296717, A2 (Lilly, Eli, and Co.) 28.12月.1988(28.12.88) & JP, 63-307894, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.111:58271 especially, compounds of RN:105882-69-7, 105882-72-2 121590-61-2	1, 24-26, 35, 37-39 / 1-52
X / Y	KIBWAGE I. O., et al,' Identification of novel erythromycin derivatives in mother liquor concentrates of Streptomyces erythraeus.' J. Antibiot., 1987, Vol.40, No.1, pages 1 to 6 & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.106:172535 especially, compounds of RN:107745-55-1, 105882-69-7	1, 2, 24-26 / 1-52
X / Y	EP, 937734, A1 (Solvay Pharmaceuticals G.m.b.H.) 25.8月.1999(25.08.99) & DE, 19805822, A & JP, 11-269193, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.131:144790 especially, compounds of RN:236099-91-5, 151052-42-5	1, 24-26 / 1-52
X / Y	WO, 92/18134, A1 (Abbott Laboratories) 29.10月.1992(29.10.92) & EP, 579770, A1 & JP, 6-509326, A & US, 5538961, A & US, 5523418, A & US, 5523401, A & US, 5554605, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.118:101716 especially, compounds of RN:105882-69-7, 145692-88-2, 145692-89-3, 145692-94-0, 145692-95-1, 145692-97-3, 145693-00-1, 145693-01-2, 145693-02-3, 145693-03-4, 145774-00-1	1, 24-26 / 1-52

(続葉頁有り)

C（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X ／ Y	EP,349100,A2 (Lilly, Eli, and Co.) 3.1月.1990(03.01.90) & US,4920102,A & JP,1-311096,A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH,USA), DN.113:59777 especially, compounds of RN:105882-69-7,127931-39-9, 127966-89-6	1,24-26 ／ 1-52

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 31/70, C07H 17/08 — A1

(11) International Publication Number: WO 92/18134

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(30) Priority data:
682,836 9 April 1991 (09.04.91) US

(60) Parent Application or Grant
(63) Related by Continuation
US 682,836 (CIP)
Filed on 9 April 1991 (09.04.91)

(71) Applicant *(for all designated States except US)*: ABBOTT LABORATORIES [US/US]; Chad 377/AP6D, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

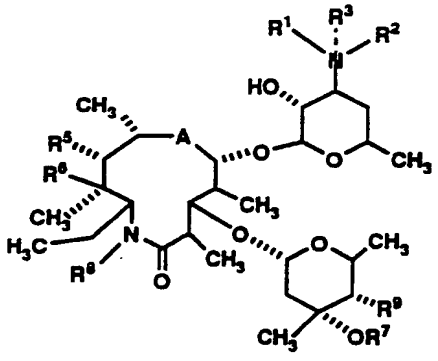
(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : FREIBERG, Leslie, A. [US/US]; 10066 West Hendee, Waukegan, IL 60087 (US). EDWARDS, Carla [US/US]; 1414 Maple Avenue, Evanston, IL 60201 (US). PARIZA, Richard, J. [US/US]; 420 Russell Avenue, Winthrop Harbor, IL 60096 (US). NELLANS, Hugh, N. [US/US]; 27272 Chevy Chase Road, Mundelein, IL 60060 (US).

(74) Agents: GORMAN, Edward, H., Jr. et al.; Abbott Laboratories, Chad 0377/AP6D-2, One Abbott Park Road, Abbott Park, IL 60064-3500 (US).

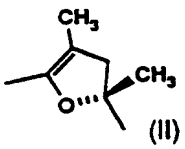
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: MACROCYCLIC LACTAM PROKINETIC AGENTS



(I)



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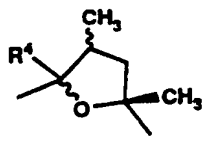

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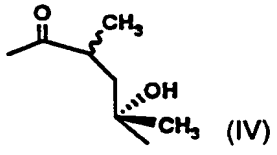

(IV)

(57) Abstract

Macrocyclic lactam compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein A is selected from (II), (III) and (IV); also disclosed are synthetic processes and intermediates useful in the preparation of the compounds of the invention, as well as compositions containing the same and methods for their use in stimulating contractile motion of the gastrointestinal tract.

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MACROCYCLIC LACTAM PROKINETIC AGENTS

This application is a continuation-in-part of copending US application Serial No. 07/682,836, filed on April 9, 1991.

TECHNICAL FIELD

This invention relates to novel macrocyclic lactam derivatives of erythromycins A, B, C and D and pharmaceutical compositions containing these compounds, as well as the use thereof in treating gastrointestinal disorders and in facilitating the placement of diagnostic and therapeutic instrumentation into the proximal small intestine. The invention also relates to processes for preparing these compounds and synthetic intermediates employed therein.

BACKGROUND OF THE INVENTION

The primary function of the alimentary or gastrointestinal (GI) tract is to provide the body with a balanced supply of water, electrolytes and nutrients. In order for this to be achieved, food must be moved along the GI tract at an appropriate rate for digestion, absorption and secretion to take place. Food is normally transported through the GI tract in a well-coordinated manner by propulsive movements which are mediated by clusters of smooth muscle contractions known as migrating myoelectric complexes, in a process commonly referred to as peristalsis.

Defects in the normal motility pattern can lead to the development of chronic, painful and debilitating disorders. For example, an incompetent or weak lower esophageal sphincter may result in frequent reflux of ingested food from the stomach into the esophagus which may lead to esophagitis. Prokinetic agents (also called motility-enhancing agents) are useful in treating reflux esophagitis because they (a) increase the pressure of the lower esophageal sphincter, thereby inhibiting reflux; (b) increase the force of esophageal peristalsis to facilitate clearance of food from the esophagus into the stomach; and (c) increase gastric emptying, thereby further decreasing the mass available for reflux.

There is a need, however, for improved prokinetic agents in the treatment of this disorder. Presently used cholinergic drugs such as bethanechol and dopamine receptor blocking agents such as metoclopramide may exhibit serious disadvantages. Bethanechol, for example, should be avoided by elderly patients while metoclopramide has a narrow therapeutic index, pronounced central nervous system (CNS) side effects and is known to stimulate prolactin release.

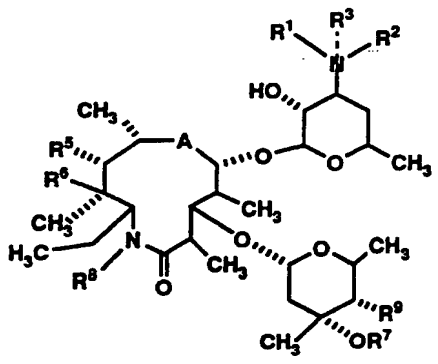
Patients suffering from other GI motility-related disorders such as delayed gastric emptying, diabetic gastroparesis, anorexia, gall bladder stasis, surgically induced adynamic ileus and chronic constipation (colonic inertia) may also benefit from treatment with prokinetic agents. In addition, prokinetic agents can aid in the placement of diagnostic and therapeutic instrumentation, such as during the insertion of enteral feeding tubes into the proximal small intestine.

Another, less common but very painful and disruptive GI motility disorder is chronic intestinal pseudoobstruction. Patients who are severely afflicted with this problem cannot tolerate oral feedings and require total parenteral nutrition. Metochlopramide and bethanecholine are also used in the treatment of this disorder but often with disappointing results. Prokinetic agents could not only be useful in alleviating the distress associated with this disorder, but also in severe cases could be used to facilitate treatment by decompression of the upper GI tract by nasogastric tubal aspiration. Increased gastric motility brought about by the use of a prokinetic agent has been shown to facilitate the placement of the necessary tubes into the intestine.

Macrocyclic lactone (macrolide) prokinetic agents are known. For example, J.S. Gidda *et al.*, in European Patent Application No. 0349100, published January 3, 1990, disclose 12-membered macrolides for use as gastrointestinal motility enhancers. S. Omura and Z. Itoh, in U.S. Patent No. 4,677,097, issued June 30, 1987, European Application No. 215,355, published March 25, 1987, and European Application No. 213,617, published March 11, 1987, disclose derivatives of erythromycins A, B, C and D which are useful as stimulants of digestive tract contractile motion. However, the compounds of these references are distinct from those of the present invention, in which novel lactam derivatives of the erythromycins are disclosed which possess an unexpected degree of prokinetic activity.

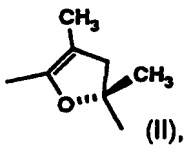
SUMMARY OF THE INVENTION

In one aspect of the present invention are provided macrocylic lactam prokinetic agents of formula (I)

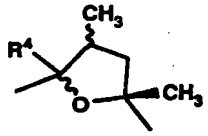


(I)

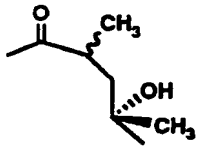
and pharmaceutically acceptable salts thereof wherein the dotted line is an optional bond. In formula (I), A is selected from



(II),



(III) and



(IV),

where a wavy line represents a bond having either steric orientation.

R^1 and R^2 in formula (I) may independently be selected from hydrogen, loweralkyl, halo-substituted loweralkyl, cyano-substituted loweralkyl, hydroxy-substituted loweralkyl, loweralkenyl, loweralkynyl, lower cycloalkyl, lower cycloalkylmethyl and benzyl.

R^3 in formula (I) may be absent or, if present, selected from loweralkyl, loweralkenyl, loweralkynyl and benzyl and accompanied by a pharmaceutically acceptable counterion so as to form a quaternary ammonium salt.

R^4 in formulae (I) and (III) may be hydrogen or, taken together with R^6, may form an ether bridge.

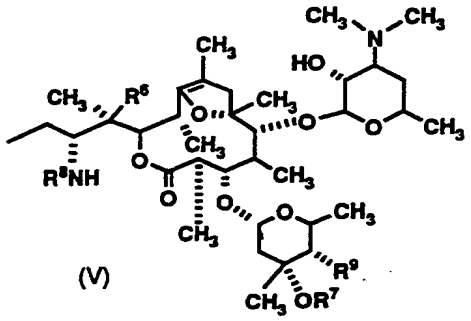
R^5 in formula (I) may be -OH, or $-OR^{10}$, wherein R^{10} is selected from loweralkyl, loweralkanoyl and $-S(O)_2CH_3$, or, taken together with R^6 and the carbons to which they are attached, may form a cyclic carbonate.

R^6 in formula (I) may be hydrogen, -OH, or $-OR^{11}$ wherein R^{11} is selected from loweralkyl, loweralkanoyl and $-S(O)_2CH_3$; or, taken together with R^4, may form an ether bridge; or, taken together with R^5 and the carbons to which they are attached, may form a cyclic carbonate.

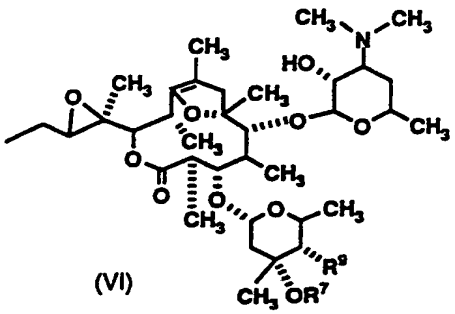
R^7 in formula (I) may be either hydrogen or methyl.

R^8 in formula (I) may be hydrogen or loweralkyl.
R^9 in formula (I) may be hydrogen or hydroxy.

In another aspect of the present invention are provided synthetic processes for preparing the compounds of the invention, as well as novel intermediates of formulae (V) and (VI)



(V)



(VI)

useful therein wherein R^6 is -OH or hydrogen, R^7 is hydrogen or methyl, R^8 is hydrogen or loweralkyl and R^9 is hydrogen or hydroxyl. The lactam compounds of the invention may be prepared directly from such intermediates, as by inducing ring closure of the amine alcohol of formula (V) or by an epoxide opening and spontaneous cyclization of the epoxide of formula (VI). Alternatively, the epoxide intermediate may first be converted to an azido alcohol and then reduced to the above amine alcohol before ring closure is induced.

In a further aspect of the present invention are provided pharmaceutical compositions for stimulating contractile motion of the gastrointestinal tract comprising a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier.

In yet another aspect of the present invention is provided a method of treating disorders characterized by impaired gastrointestinal motility such as esophageal reflux, diabetic gastroparesis, pediatric gastroparesis, postoperative paralytic ileus, intestinal pseudoobstruction, gallbladder stasis, anorexia, gastritis, emesis and chronic constipation, comprising administering to a human or lower mammal in need of such treatment a therapeutically effective amount of a compound of the invention. In a related aspect, the present invention provides a method of

facilitating the placement of diagnostic and therapeutic instrumentation, such as enteral feeding tubes, into the proximal small intestine comprising administering to a human or lower mammal in need of such treatment a therapeutically effective amount of an inventive compound.

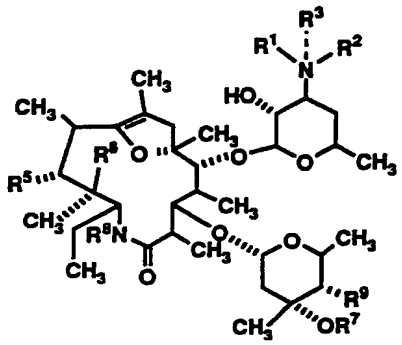
DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises novel compounds of formula (I) and the pharmaceutically acceptable salts thereof which are gastrointestinal prokinetic agents. The compounds of the present invention did not exhibit antibacterial activity in *in vitro* screening assays. These compounds are synthetic lactam derivatives of erythromycins A through D; accordingly, substituents R^6 and R^7 of the formulae herein are initially determined, as shown below, by the particular erythromycin used as starting material:

Erythromycin	Resulting R^6	Resulting R^7
A	-OH	methyl
B	hydrogen	methyl
C	-OH	hydrogen
D	hydrogen	hydrogen

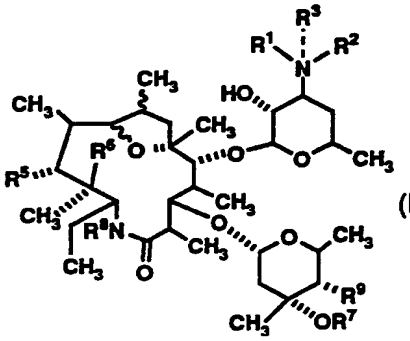
However, such lactams may be further derivatized, using well-known synthetic methodology, to obtain compounds of the invention having other substituents R^6 as well.

One class of compounds of the present invention, formed when A of formula (I) is a group of formula (II), may be represented by the formula



(I a)

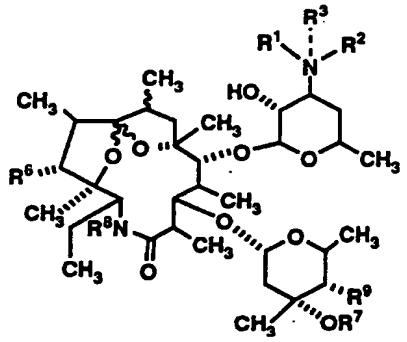
Another class of compounds of the invention, formed when A is a group of formula (III) in which R^4 is hydrogen, may be represented by the formula



(I b)

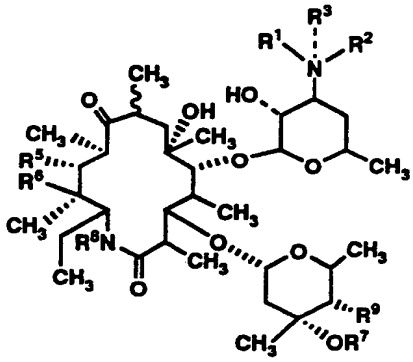
wherein, as elsewhere throughout this application, a wavy line represents a bond having either steric orientation.

A corresponding subclass of compounds of the invention occurs when R^4 of formula (III), together with R^6, forms an ether linkage; these compounds may be represented by the formula



(I c)

Yet another class of compounds of the present invention, formed when A is a group of formula (IV), may be represented by the formula



(1 d)

Representative compounds of the present invention include [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin A lactam enol ether");

[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin B lactam enol ether");

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methyl(2-propenyl)amino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethyl(2-propenyl)ammonium)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabi-cyclo[10.2.1]pentadec-14-en-7-one bromide;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one 13-O,14-O-carbonate;

[1R-(1R*2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*,14S*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadecan-7-one;

[1R-(1R*, 2R*, 3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*,14S*)]-9-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15,16-dioxatricyclo[10.2.1.1^{1,4}] pentadecan-7-one;

[3R-(3R*,4S*,5S*,6R*,7R*,9S*,11R*,12R*,13R*,14R*)]-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]azacyclotetradecane-2,10-dione ("erythromycin A lactam");

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin C lactam enol ether");
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin D lactam enol ether");
[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*n*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*n*-propylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-propylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one; and
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

as well as pharmaceutically acceptable salts thereof.

Preferred compounds of the present invention include
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin A lactam enol ether");
[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin B lactam enol ether");
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-
14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethyl(2-propenyl)ammonium)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabi-cyclo[10.2.1]pentadec-14-en-7-one bromide;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one; and
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

as well as pharmaceutically acceptable salts thereof.

The following terms are used as defined below throughout this disclosure and in the appended claims:

The term "carboxylate" as used herein refers to the anion of an organic carboxylic acid such as acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, music, D-glutamic, d-camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

The term "cyano-substituted loweralkyl" as used herein refers to a loweralkyl group as defined below which has one hydrogen atom replaced by a cyano substituent, as for example cyanomethyl or cyanoethyl.

The term "halogen" refers to chloro (Cl), bromo (Br), fluoro (F) and iodo (I).

The term "halo-substituted loweralkyl" refers to a loweralkyl group as defined below which has one, two or three halogen substituents, as for example

fluoroethyl, difluoroethyl, chloromethyl, trifluoroethyl and the like.

The term "hydroxy-substituted loweralkyl" refers to a loweralkyl group as defined below which has one hydrogen atom replaced by a hydroxy substituent, as for example hydroxymethyl or hydroxyethyl.

The term "loweralkanoyl" refers to a substituent of formula $R^{10}C(O)$- wherein R^{10} is hydrogen or a loweralkyl group as defined below.

The term "loweralkenyl" refers to straight or branched chain hydrocarbon groups containing from two to six carbon atoms and possessing at least one carbon-carbon double bond. Examples of loweralkenyl groups include vinyl, allyl, 2- or 3-butenyl, 2-,3- or 4-pentenyl and isomeric forms thereof. The double bond(s) can be in either the *cis* or the *trans* configuration.

The term "loweralkyl" refers to branched or straight chain alkyl groups comprising one to six carbon atoms including, but not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *t*-butyl, neopentyl and the like.

The term "loweralkynyl" refers to hydrocarbon groups containing from two to six carbon atoms and possessing at least one carbon-carbon triple bond. Examples of loweralkynyl groups include ethynyl, propargyl and butynyl.

The term "lowercycloalkyl" refers to cyclic hydrocarbons having three to six ring carbon atoms.

The term "delayed gastric emptying" as used herein refers to a slow evacuation of gastric contents into the small intestine not caused by mechanical obstruction of the gastric outlet. Patients with severe gastric motor dysfunction may be incapacitated from intractable nausea, vomiting and gastric stasis. This may lead to failure to thrive in a young patient or to significant weight loss and malnutrition in adults. (cf. "Medicine for the Practicing Physician Second Edition", ed. J. Willis Hurst, Butterworth Publishers, Boston, 1988, pages 1364-66.

The term "gastroparesis" refers to paralysis of the stomach.

The term "intestinal pseudoobstruction" refers to a condition characterized by constipation, colicky pain and vomiting, but without evidence of organic obstruction apparent at laparotomy (abdominal surgery).

The term "paralytic or adynamic ileus" refers to obstruction of the intestines resulting from inhibition of bowel motility.

The term "reflux esophagitis" refers to inflammation of the esophagus as a result of frequent or chronic backward or return flow of stomach contents into the esophagus.

By "pharmaceutically acceptable salts" is meant those acid addition salts of the compounds of of formula (I) which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use.

Pharmaceutically acceptable salts are well known in the art . For example, S. M Berge *et al.* describe pharmaceutically salts in detail in *J. Pharmaceutical Sciences*, 1977, vol. 66, pages 1-19. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include nitrate, bisulfate, borate, formate, butyrate, valerate, 3-phenylpropionate, camphorate, adipate, benzoate, oleate, palmitate, stearate, laurate, lactate, fumarate, ascorbate, aspartate, nicotinate, p-toluenesulfonate, camphorsulfonate, methanesulfonate, 2-hydroxyethanesulfonate, gluconate, glucoheptonate, lactobionate, glycerophosphate, pectinate, lauryl sulfate, alginate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, hemisulfate, heptonate, hexanoate, 2-naphthalenesulfonate, pamoate, persulfate, pivalate, propionate, undecanoate salts and the like, and may be prepared according to conventional methods. Representative alkali or alkaline earth metal salts include sodium, calcium, potassium, magnesium salts and the like. Pharmaceutically acceptable counterions for the quaternary ammonium salt compounds formed when R^3 is present include halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and arysulfonate.

As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol;

polyols such as glycerin, sorbitol, mannitol and polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible substances used in pharmaceutical formulations. Wetting agents, emulsifiers and lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgement of the formulator.

By a "therapeutically effective amount" of a compound of the invention is meant a sufficient amount of the compound to treat a gastrointestinal disorder, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

The total daily dose of the compounds of this invention administered to a human or other mammal in single or in divided doses can be in amounts, for example, of from about 0.01 to about 25 mg/kg body weight or, more usually, from about 0.1 to about 15 mg/kg body weight. Single dose compositions may contain such amounts or submultiples thereof as make up the daily dose. In general, treatment regimens according to the present invention comprise administration to a patient in need of such treatment of from about 10 mg to about 1000 mg of the compound(s) of this invention per day in multiple doses or in a single dose.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water. Such compositions may also comprise adjuvants such as wetting agents; emulsifying or suspending agents and sweetening, flavoring or perfuming agents.

Injectable preparations, as for example sterile injectable aqueous or

oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, as for example in solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may be used in the preparation of injectables.

The injectable formulation can be sterilized, as for example by filtration through a bacteria-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

In order to prolong the effect of a drug, it is often desirable to slow the absorption of a drug from subcutaneous or intramuscular injection. The most common way to accomplish this is to inject a suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug becomes dependent on the rate of dissolution of the drug which is, in turn, dependent on the physical state of the drug, as for example, its crystal size and crystalline form. Another approach to delaying absorption of a drug is to administer the drug as a solution or suspension in oil. Injectable depot forms can also be made by forming microcapsule matrices of drugs and biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer and the composition of the polymer, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly-orthoesters and polyanhydrides. The depot injectables can also be made by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, prills and granules. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings and other

release-controlling coatings.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such exipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be combined in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferably, in a certain part of the intestinal tract, optionally in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

The compounds of the present invention may be synthesized by the reaction schemes I through VII presented below, in which A and R^1-R^9 correspond to the groups defined with respect to formula (I). However, it should be noted that, prior to ring closure and formation of a lactam, R^6 in the following schemes is limited to hydrogen and -OH. Moreover, it will be observed that certain schemes, such as Scheme IA, are useful only where R^6 is -OH.

Scheme I

Erythromycin A or C is treated with a suitable reagent for acetylating the 2'-hydroxyl group, such as acetic anhydride or acetyl chloride, in the presence of a suitable base, such as triethylamine, pyridine or DMAP. The resulting 2'-O-acetyl compound is converted to a ring-contracted compound of Formula *3* by treatment with an appropriate nonaqueous acid, such as glacial acetic acid followed by treatment with a suitable base, preferably in a polar solvent, as for example treatment with potassium carbonate in DMF or ammonium acetate in methanol. Alternatively, compounds of Formula *1* are converted directly into the compounds of Formula *3* by the procedure described in Scheme 1A below.

The compound of Formula *3* is, in turn, converted to the epoxide of Formula *4* by treatment with bis[*a*,*a*-bis(trifluoromethyl)benzene-methanolato]-diphenyl sulfur (Martin sulfurane). Alternately the hydroxy group on carbon number 13 is activated by treatment with a suitable reagent, as for example methanesulfonyl chloride, and

the activated ester is displaced to form an epoxide upon treatment with a suitable base, as for example sodium or potassium hydroxide or sodium or potassium methoxide or *t*-butoxide, sodium or potassium carbonate. The epoxide ring of the compound of Formula *4* is then opened to form an azido alcohol of Formula *5* by treatment with a nucleophilic hydrozoic acid derivative, such as sodium azide or potassium azide. The azido alcohol is, in turn, converted to an amino alcohol of Formula *10* by treatment with a suitable reducing agent, as for example by hydrogenation in the presence of a catalyst such as Raney nickel, palladium on carbon or platinum oxide, treatment with zinc in acetic acid, or treatment with lithium aluminum hydride. The amino alcohol is cyclized to form a lactam of Formula IA by treatment with a suitable base in a suitable solvent such as ammonium hydroxide in methanol or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene.

Scheme IA

According to scheme IA, which is the preferred scheme for the synthesis of compounds of Formula 11, the compounds of Formula 1 are reacted in a two-part procedure to convert them into compounds of Formula 3. The compound of Formula 1 is first treated with a strong organic acid, as for example acetic acid, dichloroacetic acid, difluoroacetic acid, trichloroacetic acid or glycolic acid in a polar organic solvent such as methanol, DMF or acetonitrile. The reaction intermediate is not isolated, but treated directly with a suitable base such as ammonium acetate or potassium carbonate in a suitable organic solvent, such as methanol, DMF or acetonitrile, to form the compound of Formula 3. Preferred reagents are dichloroacetic acid in acetonitrile, followed by potassium carbonate in an aqueous mixture of acetonitrile and methanol. The compounds of Formula *3* are then converted to epoxides of Formula *4* by the methods described above in reaction scheme I. These epoxides are subsequently treated with an amine, as for example ammonia or methylamine and preferably in a polar solvent, to afford the compounds of Formula *11*. More preferably, the compounds of Formula *4* are treated with a methanolic solution of the appropriate amine.

Scheme II

2'-O-Acetyl erythromycin (A, B, C or D) is treated with a suitable reagent for

protecting the 4"-hydroxyl group, such as benzyloxycarbonyl chloride, in the presence of a suitable base, such as dimethylaminopyridine. The reaction is carried out in an inert solvent such as methylene chloride and preferably at a low temperature, more preferably at -25°C, to afford a 2'-O-acetyl-4"-O-benzyloxycarbonyl erythromycin derivative. This compound is optionally treated with methanol to remove the acetyl group and is treated sequentially with a suitable nonaqueous acid, such as glacial acetic acid, and a suitable base, such as potassium carbonate in DMF or ammonium acetate in methanol, to afford a compound of Formula *6*. A compound of Formula *6* is optionally treated with a suitable reagent for reacetylating the 2'-hydroxyl group and is treated with a suitable oxidizing agent such as N-chlorosuccinimide/dimethyl sulfide/triethylamine or tetrapropylammonium perruthenate/N-methylmorpholine N-oxide to give a ketone of Formula *7*. If the acetyl group is present it is removed with methanol, and the protecting group on the 4"-hydroxyl group is removed (preferably by hydrogenolysis, if the protecting group is CBZ) to give a compound of Formula *8*.

The ketone of Formula *8* is converted to an oxime of Formula *9* by treatment with hydroxylamine in the presence of a suitable base such as triethylamine. The oxime of Formula *9* is reduced under suitable conditions, as for example 4 atmospheres of hydrogen over a catalyst such as Raney nickel to afford a mixture of stereoisomers of the amino compounds of Formula *10* (in which the amino bond is shown as a wavy line to represent both steric orientations). One isomer of the amino compound is cyclized to a lactam of Formula *11* by treatment with a suitable base in an appropriate solvent, as for example ammonium hydroxide in methanol or DBU in toluene.

Scheme III

According to reaction scheme III, an erythromycin lactam of Formula *11* is treated with iodine and light in the presence of a suitable base, such as sodium acetate, to afford a N-demethyl derivative of Formula *12*. A compound of Formula *12* is, in turn, treated with a suitable alkylating agent such as allyl bromide to afford a compound of Formula *13*. Alternatively, a compound of Formula *12* is treated with an appropriate aldehyde to give an imine which is reduced (preferably *in situ*) by hydrogenation in the presence of a suitable catalyst as for example, palladium on carbon, to afford a compound of Formula *13*. The compounds of Formula *13* are treated with iodine and light in the presence of a suitable base, for example sodium

acetate, to afford the N-demethyl derivative of Formula *14*. A compound of Formula *14* is, in turn, treated with a suitable alkylating agent such as allyl bromide to afford a compound of Formula *15*. Alternatively, a compound of Formula *14* is treated with an appropriate aldehyde, as for example acetaldehyde, to give an imine which is reduced (preferably *in situ*) by hydrogenation in the presence of a suitable catalyst, as for example palladium on carbon, to afford a compound of Formula *15*.

Other alkylating agents which may be used in preparing compounds of Formula *13* and Formula *15* are loweralkyl halides such as ethyl bromide, halo-substituted loweralkyl halides, cyano-substituted loweralkyl halides, hydroxy-substituted loweralkyl halides, other loweralkenyl halides such as methylallyl chloride, loweralkynyl halides such as propargyl bromide, lower cycloalkyl halides, lower cycloalkylmethyl halides such as lower cyclopropylmethyl and benzyl halides.

Scheme IV

According to reaction scheme IV, an erythromycin lactam derivative of Formula *11* or *15* is treated with an a loweralkyl halide such as methyl iodide or ethyl bromide, a loweralkenyl halide such as allyl bromide, a loweralkynyl halide such as propargyl bromide or a benzyl halide such as benzyl bromide to afford a quaternary salt derivative of Formula *16*.

Scheme V

According to reaction scheme V, an erythromycin A or C lactam of Formula *11* or *15* (wherein R^5 and R^6 are both OH) is treated with a suitable carbonic acid derivative such as ethylene carbonate, carbonyl diimidazole or thiocarbonyl diimidazole to afford a carbonate derivative of Formula *17*. Methods for preparing the loweralkanoyl and $-S(O)_2CH_3$ derivatives (compounds of formula (I) wherein R^5 or R^6 are loweralkanoyl and $-S(O)_2CH_3$) are well known in the art are, for example, are described by S. Omura and Z. Itoh in European Application Number 213,617, published November 3, 1987. Alternatively, reaction of a suitably protected lactam of formula 11 or 15 with a base, for example, sodium hydride, and an alkylating agent, such as methyl iodide, affords alkyl derivatives wherein R5 or R6 may be a loweralkyl group.

Scheme VI

According to reaction scheme VI, an erythromycin lactam of Formula *11* is reduced by catalytic hydrogenation using a suitable catalyst such as platinum oxide in the presence of a suitable acid such as difluoroacetic acid in a suitable solvent, preferably acetic acid, to afford the compounds of Formula *18*.

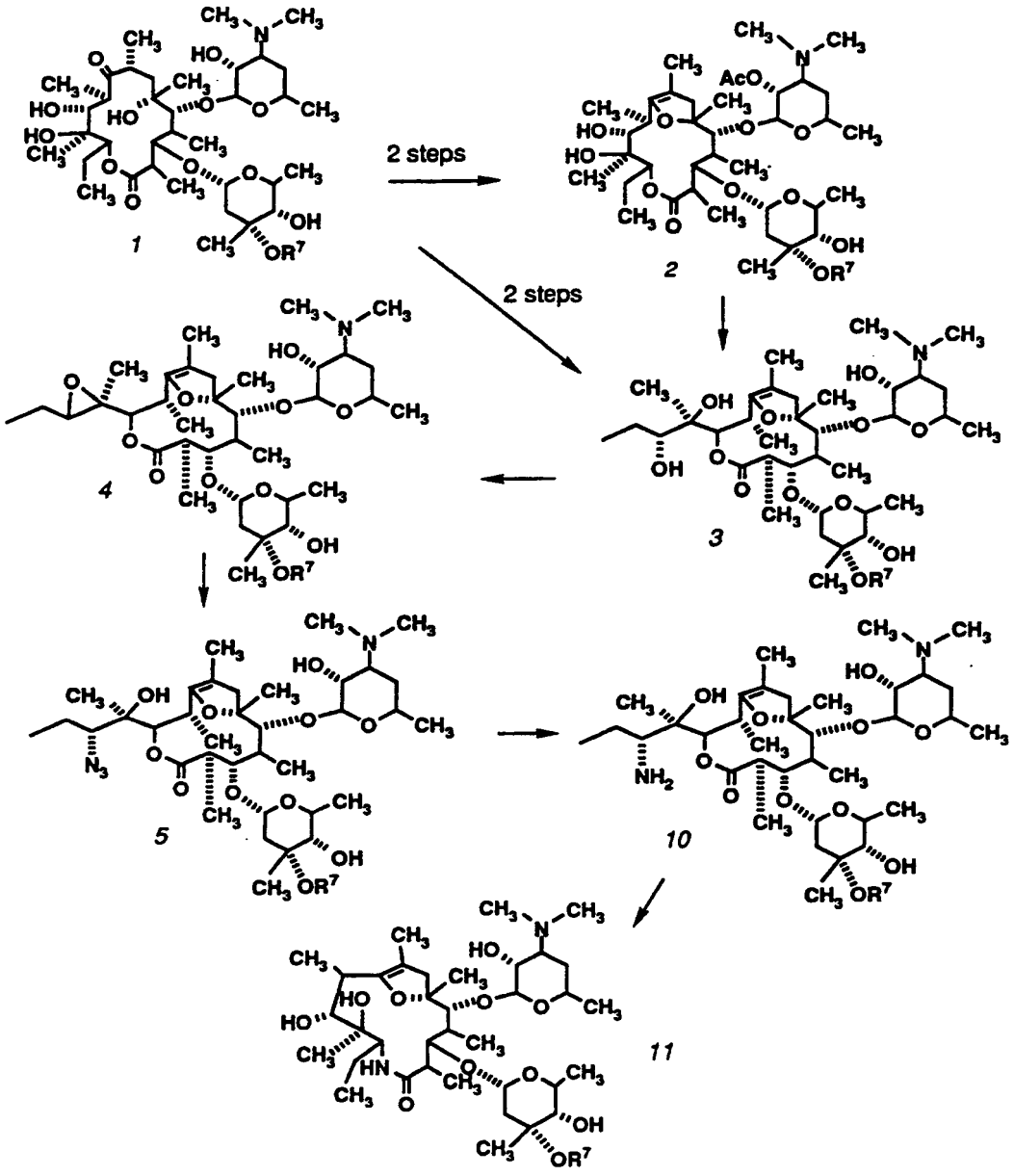
Scheme VII

According to reaction scheme VII, an erythromycin lactam of Formula *11* (wherein R^6 is OH) is treated with aqueous acid to afford a mixture of compounds which includes the compounds of Formulas *19* and *20*. The compounds of Formulas *19* and *20* (wherein wavy lines indicate both stereoisomers are formed) are also formed *in vivo* when compounds of Formula *11* are exposed to the acidic conditions of the stomach.

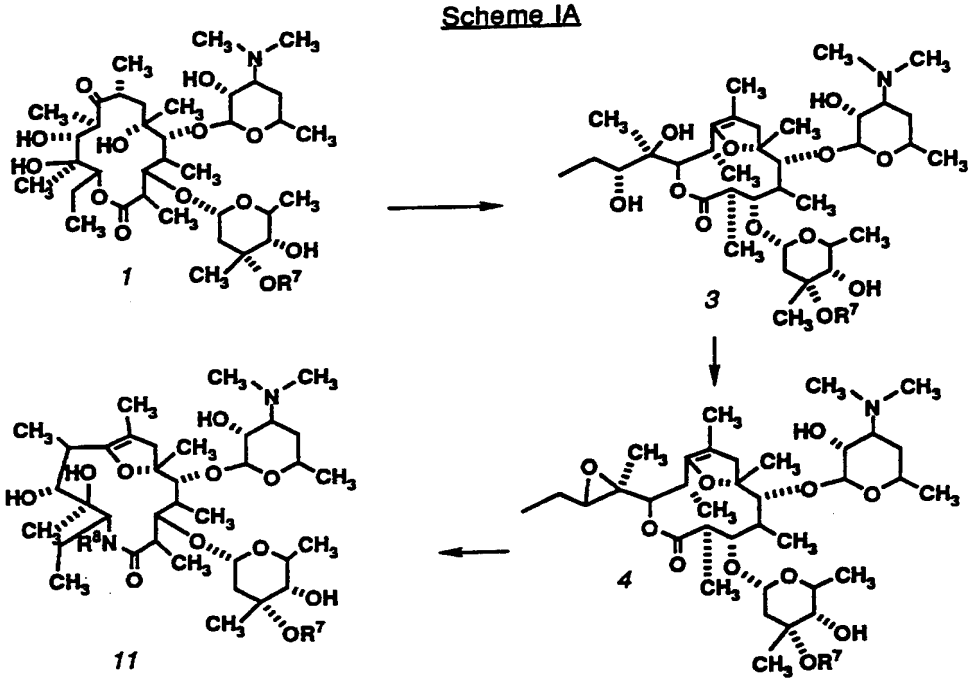
Scheme VIII

According to Scheme VIII, the ring-contracted epoxide compound of Formula *4* is treated with a suitable reagent for acetylating the 2'-hydroxyl group, such as acetic anhydride or acetyl chloride, in the presence of a suitable base, such as triethylamine, pyridine or DMAP. The compound of Formula *21* is converted to the 4"-deoxy compound by treatment with 1,1'-thiocarbonyldiimidazole (Aldrich Chemical Co., Milwaukee, Wisconsin) in the presence of a suitable base such as triethylamine, pyridine or DMAP. The compound of Formula *21* is in turn treated with a selective reducing agent, as for example tri-*n*-butyl tin hydride and AIBN (2,2'-azobis(2-methylpropionitrile), Alfa Catalog Chemicals) in an inert atmosphere to give the 4"-deoxy compound of Formula *23*. This compound is then treated with an appropriate amine, such as ammonia or methylamine, and preferrably in a polar solvent, to afford the desired 4"-deoxy lactams (compounds *24* and *25*). These compounds may optionally be further modified by the reactions described in the previous Schemes III-VII, substituting the compounds of Formula *24* or *25* for compounds of Formula *11*.

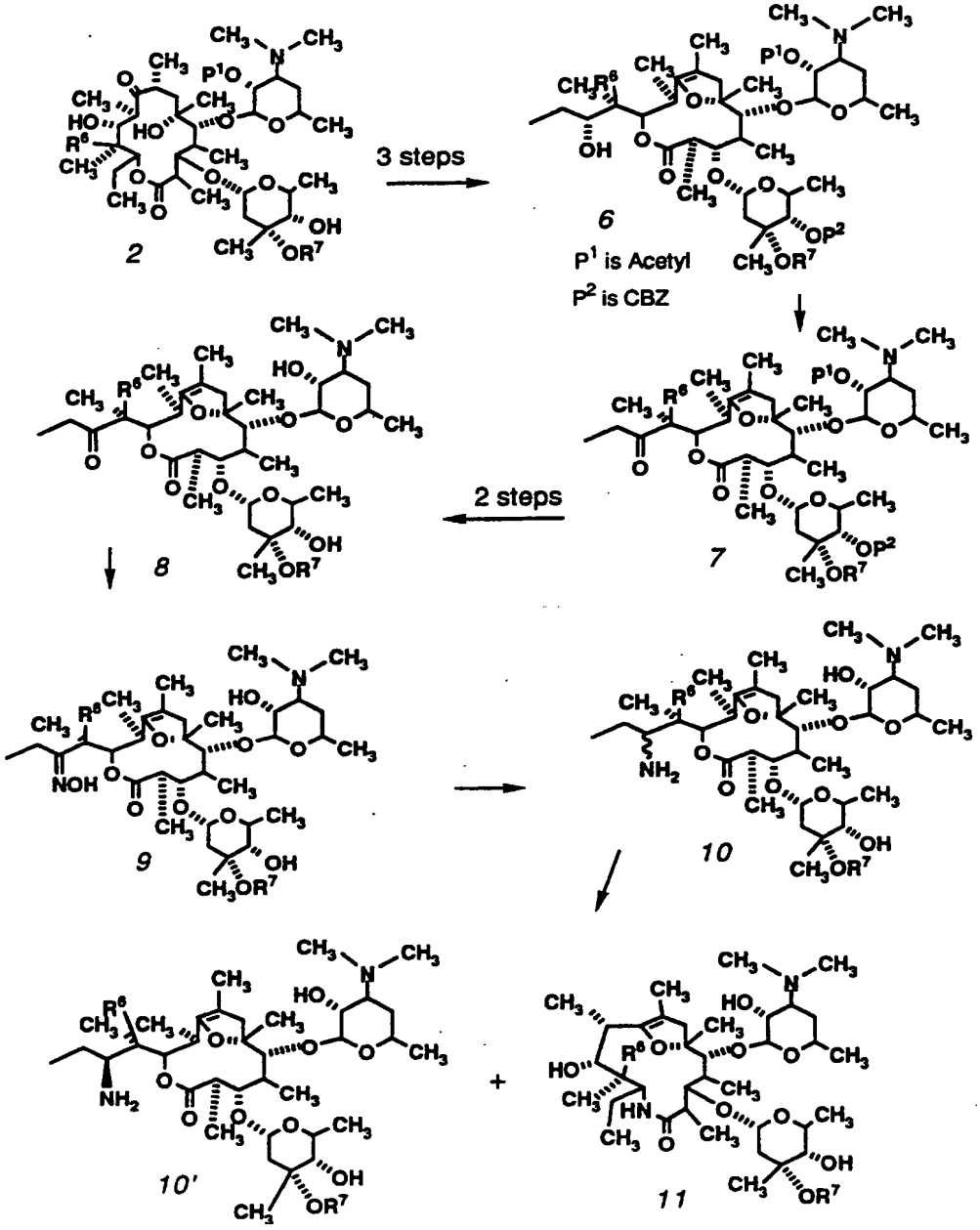
Scheme I



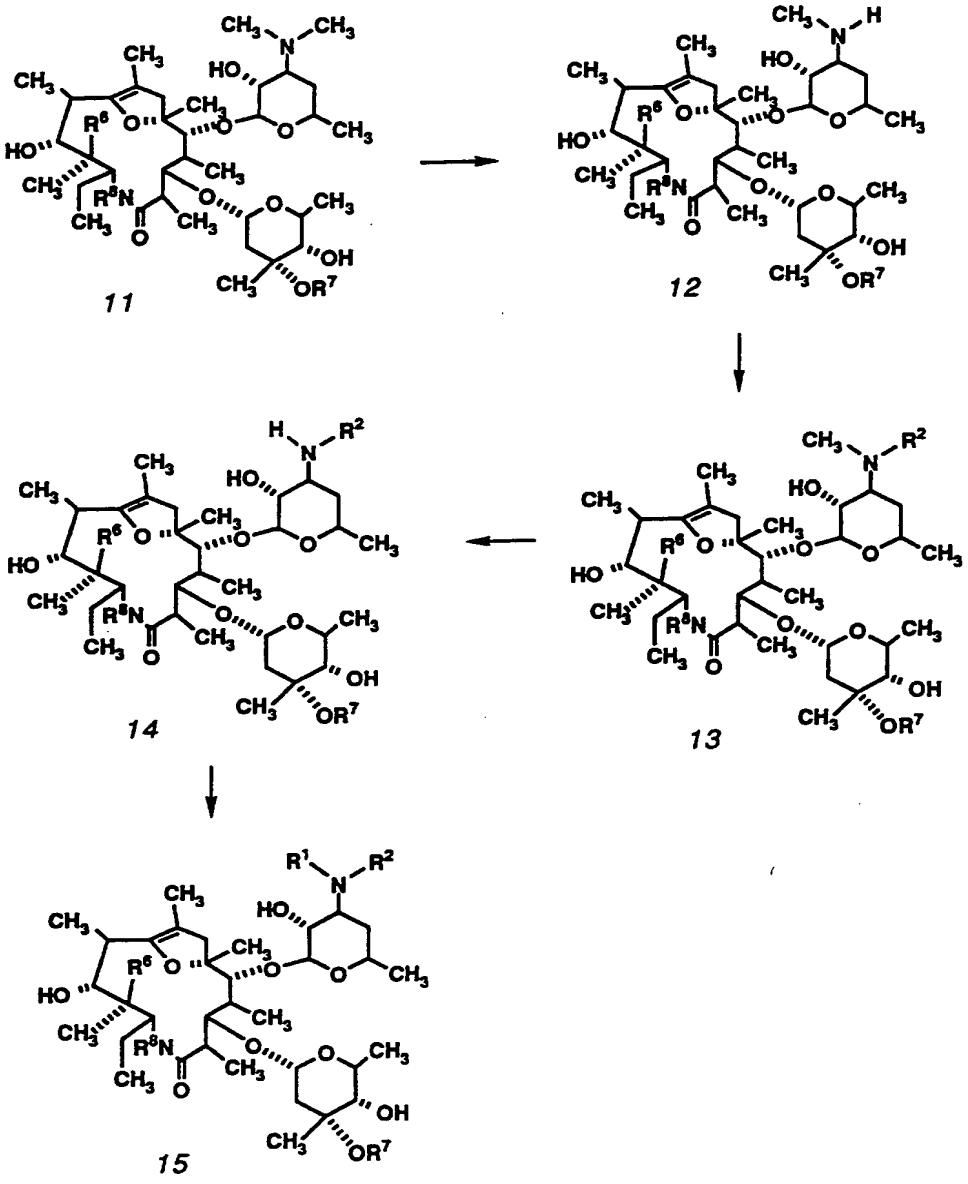
Scheme IA



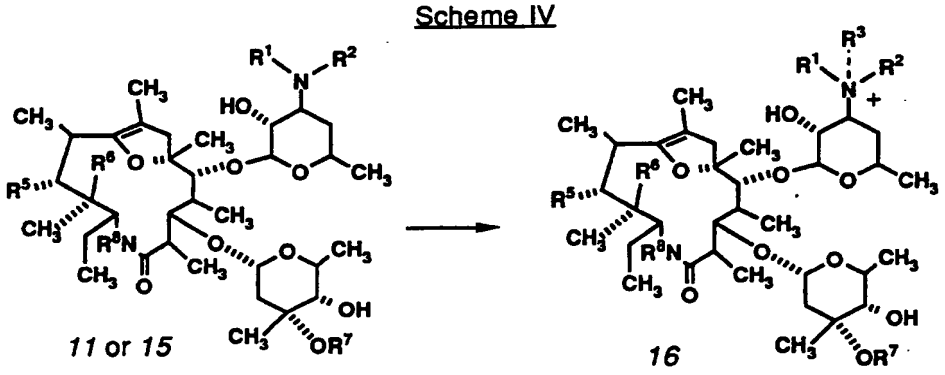
Scheme II



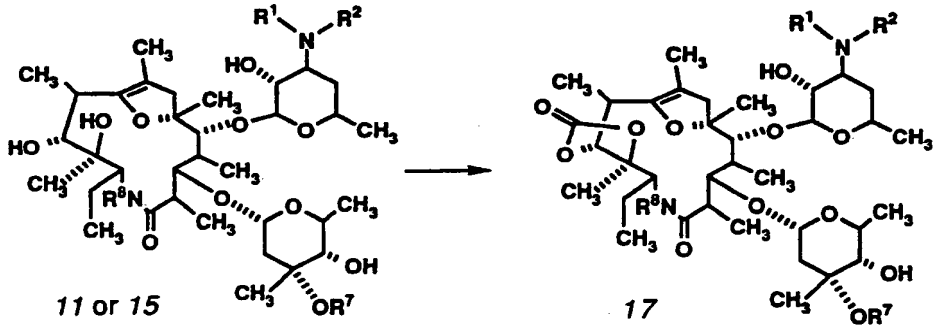
Scheme III



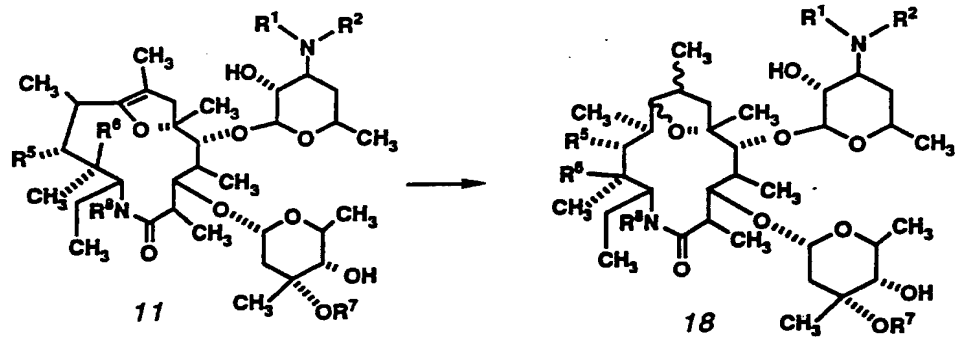
Scheme IV



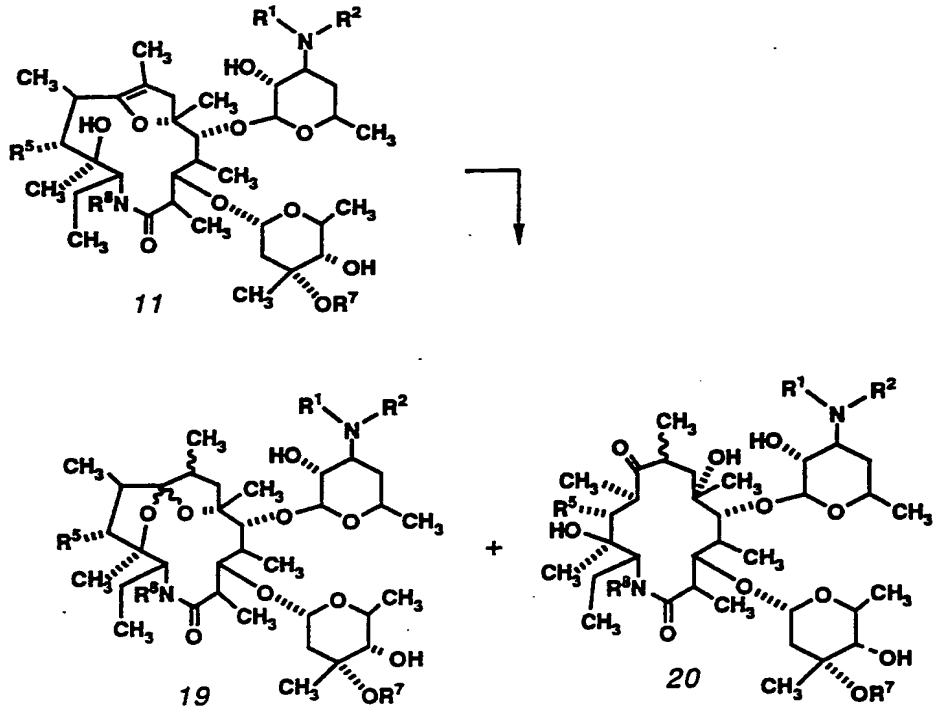
Scheme V



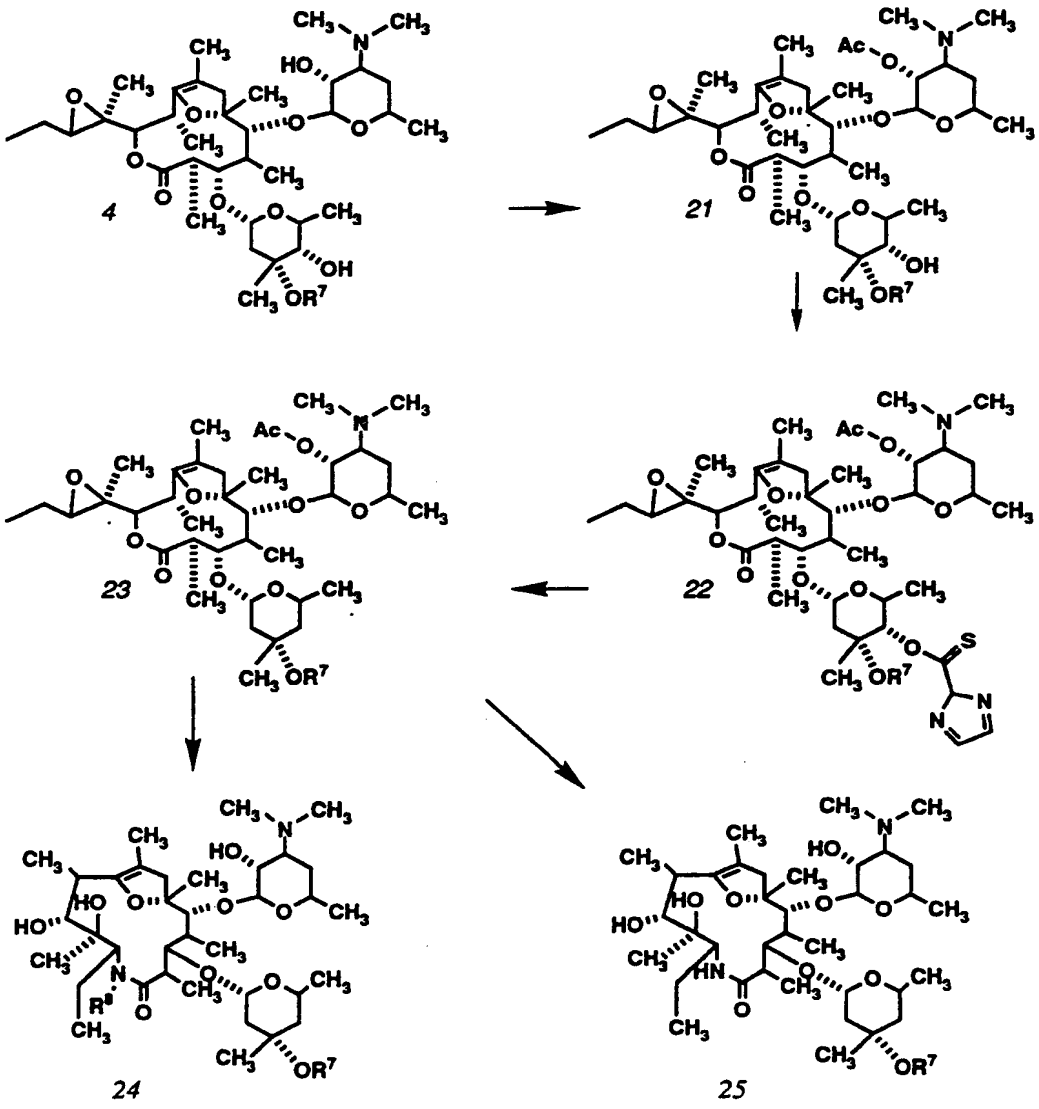
Scheme VI



Scheme VII



Scheme VIII



The foregoing may be better understood by reference to the following examples, which are provided for illustration only and are not intended as a limitation of the invention.

Example 1

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

Step 1: 2'-O-Acetylerythromycin A

Erythromycin A (50.0 g, 68.1 mmol) (commercially available from Abbott Laboratories) was dissolved in 600 mL of methylene chloride (CH_2Cl_2) at ambient temperature. Triethylamine (20 mL) and 10 mL (10.82 g, 106 mmol) of acetic anhydride were added to this solution. The reaction mixture was heated to reflux and 100 mL of CH_2Cl_2 was distilled from the reaction mixture to remove any traces of water. The reaction mixture was heated at reflux temperature for an additional five hours. After six hours, when the reaction was complete, according to TLC analysis, the reaction mixture was cooled to ambient temperature and transferred to a separatory funnel. The CH_2Cl_2 solution was washed with 300 mL of ammonium hydroxide/sodium bicarbonate solution containing 2.9% ammonia and 1.8% sodium bicarbonate, dried over anhydrous sodium sulfate and filtered. The CH_2Cl_2 was removed using a rotary evaporator with a water bath temperature of 30-40°C. The residue was crystallized from 200 mL of acetonitrile (CH_3CN) by first dissolving it in hot CH_3CN and allowing the solution to stand overnight at ambient temperature, then cooling it to -25°C and maintaining this temperature for 24 hours. The product was isolated as white crystals which were washed with cold (-25°C) CH_3CN and dried in a vacuum oven at 50°C for approximately 64 hours. The 2'-O-acetylerythromycin A was obtained in 83% yield (43.91 g).

Step 2: 2'-O-Acetyl-8,9-didehydro-9-deoxo-6-deoxy-6,9-epoxyerythromycin A

2'-O-Acetylerythromycin A (20 g, 25.8 mmol) from Step 1 was dissolved in 115 mL of glacial acetic acid. The resultant solution was stirred at ambient temperature for 2 hours. The acetic acid was removed *in vacuo*. The complete removal of the acetic acid was accomplished by azeotropic distillation with toluene. The residue was dissolved in 200 mL of ethyl acetate and was washed with a mixture of 100 mL of 5% aqueous sodium bicarbonate solution and 10 mL of concentrated aqueous ammonium hydroxide solution. The aqueous layer was extracted with 3 X 100 mL of ethyl acetate. The combined ethyl acetate layers were washed with 200 mL of

brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue (19.67 g) was crystallized from ethyl acetate to give 13.54 g (69 % yield) of the title compound: DCI-NH_3 MS M/Z: 758 $(M+H)^+$.

Step 3: [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

2'-O-Acetyl-8,9-didehydro-9-deoxo-6-deoxy-6,9-epoxyerythromycin A (5.75 g, 7.6 mmol) from Step 1 was dissolved in 35 mL of anhydrous N,N-dimethylformamide (DMF). Solid anhydrous potassium carbonate was finely powdered and added to the resultant solution. The suspension was stirred at ambient temperature for 3 days. The reaction mixture was diluted with ice-water (100 mL) and was extracted with ethyl acetate (1 X 150 mL and 3 X 50 mL). The combined ethyl acetate layers were washed with 100 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue (7.03 g) was chromatographed on 150 g of silica gel eluted with toluene:methanol (10:1). The residue was dissolved in methanol and the solution was left overnight at ambient temperature to cleave the acetyl group. The solution was concentrated *in vacuo* to give 1.56 g (29% yield) of the title compound; IR (0.15% in CCl_4) 3600, 3550 and 1720 cm^{-1}.

Step 4: [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (0.5 g, 0.7 mmol) from Step 3 was dissolved in 1 mL of dry methylene chloride and the resultant solution was added dropwise to a stirred solution of 0.94 g (1.4 mmol) of stirred bis[a,a-bis(trifluoromethyl)benzene-methanolato]-diphenylsulfur (Martin sulfurane; commercially available from Aldrich Chemical Company) in 1 mL of dry methylene chloride. The reaction mixture was stirred for 45 minutes and then poured into a separatory funnel containing 30 mL of ethyl acetate. Aqueous 5% sodium

bicarbonate solution (30 mL) was added until the pH of the solution was neutral. The ethyl acetate layer was separated and the aqueous mixture was extracted with 3 X 10 mL of ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a yellow oil. The residue was chromatographed on approximately 50 g of silica gel eluted sequentially with 2 L of toluene/acetone (5:1), 2,125 mL of toluene/methanol (10:1) and 1500 mL of toluene/methanol (5:2) to give 0.5 g of the title compound; DCI NH_3 MS M/Z: 698 $(M+H)^+$; IR (0.15% in CCl_4) 3555 and 1725 cm^{-1}.

Step 5: [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-3-(2-Azido-1-hydroxy-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (14.19 g, 20.3 mmol), from Step 4, was dissolved in 350 mL of 2-methoxyethanol. To this solution, with stirring, was added a solution of 10.6 g (0.163 mmol) of sodium azide and 0.853 g (0.16 mmol) of ammonium chloride in 141 mL of water. The reaction mixture was heated at reflux temperature for 5 days. The reaction mixture was transferred to a separatory funnel and 200 mL of 5% aqueous sodium bicarbonate was added. The mixture was extracted with 200 mL of methylene chloride followed by 2 X 100 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a yellow oil. The oil was chromatographed on approximately 500 g of silica gel eluted with chloroform/methanol/ammonia (10:1: 0.0125) to give 8.5 g (57% yield) of the title compound as a yellow glass; DCI NH_3 MS M/Z: 741 $(M+H)^+$; IR (0.15% in CCl_4) 3590, 3548, 3470, 2110 and 1735 cm^{-1}.

Step 6: [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-3-(2-Amino-1-hydroxy-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-3-(2-Azido-1-hydroxy-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-

2,6,8,10,12-pentamethyl-9-[[3,4,6-trid oxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (1 g, 1.35 mmol) from Step 5, 4.5 g of Raney nickel and 100 mL of methanol were combined under 4 atmospheres of hydrogen and the mixture was shaken at ambient temperature for 24 hours. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to a light-green glass. The glass (1.08 g) was dissolved in 100 mL of methylene chloride and washed with 100 mL of 5% aqueous sodium bicarbonate. The aqueous layer was extracted with 3 X 50 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to 880 mg (91% yield) of the title compound; DCI NH_3 MS M/Z: 715 $(M+H)^+$; IR (0.15% in CCl_4) 3595, 3548, 3470, and 1725 cm^{-1}. Analysis calculated for $C_{37}H_{66}N_2O_{11}$: C, 62.16; H, 9.31; N, 3.92. Found: C, 62.19; H, 9.21; N, 3.52.

Step 7: [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(di-methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo [10.2.1]pentadec-14-en-7-one

[2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-3-(2-Amino-1-hydroxy-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (0.81 g, 1.1 mmol) was dissolved in 88 mL of methanol. Ammonium hydroxide (8.5 mL) was added and the reaction mixture was stirred at ambient temperature for 24 hours. The solvent was removed *in vacuo*. Methylene chloride was added to and evaporated from the residue twice to remove residual water affording 770 mg (95% yield) of the title compound; DCI NH_3 MS M/Z: 715 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3442, 3358, 1703 and 1660 cm^{-1}.

Example 1 A

Alternate preparation of [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

Step 1: [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (the product of Step 3 of Example 1)

Erythromycin A (100 g, 136.25 mmol) was dissolved in 1 L of methanol and 62.5 mL (1090 mmol, 8 equivalents) of glacial acetic acid was added. The reaction mixture was heated to reflux and refluxed for 4.25 hours. The reaction mixture was then cooled in an ice bath and to the cooled mixture was added, dropwise over a 15 minute period, 73.5 mL (1090 mmol, 8 equivalents) of concentrated ammonium hydroxide. The reaction mixture was then brought to reflux and refluxed for 24 hours. After keeping the reaction mixture at 25°C overnight, it was concentrated to a solid mass under reduced pressure using a water bath at 55°C. The residue was taken up in a mixture of 500 mL of ethyl acetate, 400 mL of water and 100 mL of concentrated ammonium hydroxide. After stirring for approximately 20 min, the ethyl acetate layer was separated and the aqueous layer was extracted with 250 mL of ethyl acetate. The combined ethyl acetate solution was washed with 2 X 350 mL of brine and 2 X 350 mL of water, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was dried at 25°C (1 mm Hg) for 18 hours to afford 93.1 g of the crude product. The crude product was dissolved in 300 mL of acetonitrile and allowed to crystallize (4 hours at ambient temperature and approximately 65 hours at -25°C). The crystals were dried at 65°C (over P_2O_5) in a vacuum oven to give 54.2 g of the title compound, m.p. 125-130°C.

Step 2: [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (0.5 g, 0.7 mmol) from Step 1 was dissolved in 1 mL of dry methylene chloride and the resultant solution was added dropwise to a stirred solution of 0.94 g (1.4 mmol) of bis[a,a-bis(trifluoromethyl)benzene-methanolato]-diphenylsulfur (Martin sulfurane; commercially available from Aldrich Chemical Company) in 1 mL of methylene

chloride. The reaction mixture was stirred for 45 minutes and then poured into a separatory funnel containing 30 mL of ethyl acetate. Aqueous 5% sodium bicarbonate solution (30 mL) was added until the pH of the solution was neutral. The ethyl acetate layer was separated and the aqueous mixture was extracted with 3 X 10 mL of ethyl acetate. The combined ethyl acetate layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a yellow oil. The residue was chromatographed on approximately 50 g of silica gel eluted sequentially with 2 L of toluene/acetone (5:1), 2,125 mL of toluene/methanol (10:1) and 1500 mL of toluene/methanol (5:2) to give 0.5 g of the title compound; DCI NH_3 MS M/Z: 698 $(M+H)^+$; IR (0.15% in CCl_4) 3555 and 1725 cm^{-1}.

Step 3: [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo [10.2.1]pentadec-14-en-7-one

[2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (2.00 g, 2.87 mmol), from Step 2, was dissolved in 16 mL of methanol, in a heavy-walled glass reaction tube. To the resultant solution was added 4.0 mL of concentrated ammonium hydroxide (59.2 mmol ammonia, 20.6 equivalents). The tube was sealed with a Teflon® "O" ring-type-screw plug. The reaction mixture was then heated to 90-92°C in an oil bath. The progress of the reacton was followed by HPLC using a YMC reverse phase R-ODS-7 HPLC column eluted at 1.00 mL/minute with 60% aqueous methanol containing 10 g/L of ammonium acetate trihydrate, 25 mL/L glacial acetic acid and 50 mL/L of tetrahydrofuran. After 6 days, the reaction mixture was cooled to ambient temperature and then diluted with 250 mL of 8% aqueous sodium bicarbonate solution. The pH of the solution was brought to 10 by the addition of 10 mL of concentrated ammonium hydroxide and the basic solution was extracted with 3 X 50 mL portions of chloroform. The combined chloroform extracts were washed with 50 mL of a 1:1 solution of 8% aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* in a water bath at 45°C. The residue was dried at 25°C under vacuum for 3 hours to give 2.277 g of crude product. A column of silica gel (100 g), which had been washed with 1 L of 40% methanol in acetonitrile containing 2% concentrated ammonium

hydroxide and 1 L of 0.1% concentrated ammonium hydroxide in acetonitrile, was equilibrated with 0.5 L of the eluent, 10% acetonitrile in chloroform containing 3.0% methanol and 0.3% concentrated ammonium hydroxide. The crude product was then chromatographed, eluting at 2.5 mL/minute. The fractions containing the desired product were combined and concentrated *in vacuo* in a water bath at 45°C. The residue was dissolved in 50 mL of methanol and the resultant solution was filtered and concentrated *in vacuo* to give, after drying *in vacuo* at 25°C for 3 days, 1.752 g (85.4% yield) of the title compound. A sample was crystallized from acetonitrile at -25°C to give needle-like crystals, m.p. 152-156°C after drying at 1 Torr/100°C; $[\alpha]_D^{23}$ = -39.2° (c 1.00; MeOH)

Example 2

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

Step 1: 2'-O-Acetyl-4"-O-benzyloxycarbonylerythromycin A

2'-O-Acetylerythromycin A (30 g, 38.6 mmol), the product of Step 1 of Example 1, was dissolved in 150 mL of methylene chloride. Dimethylaminopyridine (18.3 g, 149.8 mmol) was added and the solution was cooled to -40°C in an acetonitrile/dry ice bath. Benzyloxycarbonyl chloride (16.8 mL, 110 mmol) was added and the solution was stirred at -40°C until a gel formed. After keeping the reaction mixture at -25°C for 3 days, the mixture was poured into a separatory funnel and was washed with phosphate buffer (pH 5.0). The organic layer was washed with 5% aqueous sodium bicarbonate. The aqueous sodium bicarbonate layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to an off-white glass. The glass was recrystallized from acetonitrile to give 21.39 g (61% yield) of the title compound; DCI NH_3 MS M/Z: 910.

Step 2: 2'-O-Acetyl-4"-O-benzyloxycarbonyl-8,9-didehydro-9-deoxo-6-deoxy-6,9-epoxyerythromycin A

2'-O-Acetyl-4"-O-benzyloxycarbonylerythromycin A (21.29 g, 23.37 mmol),

from Step 1, was dissolved in 115 mL of glacial acetic acid and the resultant solution was stirred at ambient temperature for 2 hours. The acetic acid was azeotropically removed *in vacuo* using toluene. The residue was dissolved in 500 mL of ethyl acetate and the ethyl acetate solution was washed with a mixture of 300 mL of 5% aqueous sodium bicarbonate solution and 10 mL of ammonium hydroxide. The aqueous layer was extracted with 100 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 19.39 g (93% yield) of the title compound as a white glass; DCI NH_3 MS M/Z: 892.

Step 3: [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

Following the procedures described in Step 3 of Example 1, and purifying the product by chromatography on silica gel eluted with toluene/acetone (5:1) followed by toluene/acetone (10:3), 5.3 g (5.95 mmol) of the product of Step 2 above was treated with potassium carbonate in DMF to give 1.46 g (28% yield) of the title compound; DCI NH_3 MS M/Z: 892; IR (5% in $CDCl_3$) 3595, 3560 and 1740 cm^{-1}.

Step 4: [2R-[2R*,3R*(1S*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1-hydroxy-1-methyl-2-oxobutyl)-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

N-chlorosuccinimide (0.57 g, 4.27 mmol) was dissolved in 5.05 mL of toluene and the resultant solution was cooled to -10°C. Dimethyl sulfide (0.41 mL, 5.58 mmol) was added and the solution was stirred at -10°C for 20 minutes. A solution of [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-acetyl-3,4,6-trideoxy-3'-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (0.5 g, 0.56 mmol), from Step 3, in 1.28 mL of toluene was added and the reaction mixture was stirred at -40°C for 3.5 hours. The reaction was then quenched by the addition of triethylamine and the reaction mixture was transferred to a separatory

funnel and a 5% aqueous sodium bicarbonate solution was added. The aqueous layer was extracted with 4 X 50 mL of toluene and once with 50 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 0.455 g (91% yield) of the title compound; DCI NH_3 MS M/Z: 890; IR (5% in $CDCl_3$) 3540 and 1740 cm^{-1}.

Step 5: [2R-[2R*,3R*(1S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1-hydroxy-1-methyl-2-oxobutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1S*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1-hydroxy-1-methyl-2-oxobutyl)-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (3.57 g, 4.02 mmol), from Step 4, was dissolved in 200 mL of methanol. To this solution was added 3.57 g of 10% palladium on carbon. The reaction mixture was shaken at ambient temperature under 4 atmospheres of hydrogen for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue (2.5 g) was dissolved in 200 mL of methylene chloride. The methylene chloride solution was washed with 100 mL of 5% aqueous sodium bicarbonate. The aqueous wash was extracted with 3 X 50 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 2.01 g (70% yield) of the title compound; FAB MS M/Z: 714 $(M+H)^+$.

Step 6: [2R-[2R*,3R*(1R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1-hydroxy-1-methyl-2-oximidobutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1-hydroxy-1-methyl-2-oxo-butyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (0.5 g, 0.7 mmol), from Step 5, was dissolved in 10 mL of ethyl alcohol. To this solution was added 0.39 g (6.05 mmol) of hydroxylamine hydrochloride and 0.6 mL (4.23 mmol) of

triethylamine. The reaction mixture was heated at reflux temperature for 84 hours. The reaction mixture was allowed to cool to ambient temperature and then it was poured into a separatory funnel along with 200 mL of methylene chloride and washed with 100 mL of 5% aqueous sodium bicarbonate. The aqueous layer was extracted with 2 X 50 mL of methylene chloride, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue (200 mg out of total of 410 mg) was chromatographed on 50 g of silica gel eluted with chloroform/methanol/ammonia (10:1:0.015) to give 77.8 mg of the title compound; FAB MS M/Z: 729 $(M+H)^+$; IR (0.15% in CCl_4) 3595 and 1733 cm^{-1}.

Step 7: [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

A mixture of 100 mg (0.137 mmol) of [2R-[2R*,3R*(1R*), 6R*, 7S*, 8S*, 9R*, 10R*]]-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1-hydroxy-1-methyl-2-oximidobutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one, 0.56 g of Raney nickel and 10 mL of ammonia in 90 mL of methanol was shaken at ambient temperature under 4 atmospheres of hydrogen for 24 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to a foam. The foam was dissolved in 50 mL of methylene chloride and washed with 30 mL of 5% aqueous sodium bicarbonate. The aqueous layer was extracted with 3 X 25 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 99.8 mg of the title compound; LSIMS/NBA, DMF M/Z: 715 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3440, 3355, 1703 and 1660 cm^{-1}.

Example 3

[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

Step 1: 2'-O-Acetylerythromycin B

Following the procedures described in Step 1 of Example 1, replacing erythromycin A with erythromycin B, the title compound was prepared.

Step 2: 2'-O-Acetyl-4"-O-benzyloxycarbonylerythromycin B

A mixture of 30.60 g (40.264 mmol) of 2'-O-acetylerythromycin B and 15.00 g (122.78 mmol) of dimethylaminopyridine (DMAP) was dissolved in 75 mL of methylene chloride. The resultant solution was cooled to -25°C in a dry ice/CCl_4 bath. Benzylchloroformate (11.5 mL, 56.41 mmol) was added and the mixture was stored at -25°C overnight. TLC analysis indicated incomplete reaction, therefore, DMAP (7.5 g) and benzylchloroformate (6 mL) were added and the mixture stirred at -25°C for 6 hours. The reaction mixture was then diluted with 400 mL of ethyl acetate and was washed sequentially with 2 X 100 mL of 4% aqueous sodium bicarbonate, 100 mL of brine, 3 X 100 mL of 10% aqueous potassium dihydrogen phosphate/ brine (4:1), 100 mL of brine and 100 mL of 4% aqueous sodium bicarbonate solution. The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a semi-solid glass. The residue (45.14 g) was triturated with 300 mL of heptane to give 33.44 g (93% yield) of the title compound.

Step 3: [2R-[2R*,3S*(1S*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(4-O-Benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(2-hydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8,2,1]tridec-12-en-5-one

2'-O-Acetyl-4"-O-benzyloxycarbonylerythromycin B (10.11 g, 11.307 mmol) was dissolved in 250 mL of methanol and the solution was allowed to stand at 25°C for 3 days. Glacial acetic acid (5.43 mL (94.92 mmol) was added and the resultant mixture was heated at reflux temperature for 48 hours. The reaction was then cooled to ambient temperature and 6.41 mL (94.92 mmol) of concentrated ammonium hydroxide was added. The reaction mixture was heated at reflux temperature for 9 days. The reaction mixture was concentrated to 25 mL and then diluted with 300 mL of 4% aqueous sodium bicarbonate. The aqueous mixture was extracted with 1 X 100 mL of chloroform followed by 2 X 50 mL of chloroform. The combined organic extracts were washed with 100 mL of 4% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Acetonitrile was added to the residue to azeptropically remove residual

chloroform and water and evaporated under reduced pressure to give 8.91 g of the title compound which was taken on to the next step without purification.

Step 4: [2R-[2R*,3S*(1S*,2R*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(2-hydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3S*(1S*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(4-O-Benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(2-hydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (8.84 g, 10.599 mmol), from Step 3, was dissolved in 175 mL of methylene chloride. Acetic anhydride (3.5 mL) and triethylamine (9 mL) were added and the reaction mixture was allowed to stand at ambient temperature for 2.5 days. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 200 mL of ethyl acetate. The ethyl acetate solution was washed with 4 X 50 mL of 4% aqueous sodium bicarbonate solution. Solid sodium chloride (20 mL) was added to each of the second, third and fourth washes to improve the phase separation. The ethyl acetate solution was dried over sodium sulfate, filtered and concentrated *in vacuo* to give 9.12 g of the title compound as a white glass; IR (0.15% in CCl_4): 3530, 1748 and 1718 cm^{-1}.

Step 5: [2R-[2R*,3R*(1R),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oxobutyl)-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

A mixture of 5.197 g (5.932 mmol) of [2R-[2R*,3S*(1S*,2R*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(2-hydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one from Step 4, 4.20 g (35.85 mmol) of N-methylmorpholine N-oxide and 2.5 g of 4 Å molecular sieves in 26 mL of methylene chloride was stirred at 20°C for 1 hour. The reaction mixture was then cooled to -15°C in an ice/acetone bath and after 15 minutes, 30.9 mg (0.879 mmol) of tetrapropyl-ammonium perruthenate was added. After stirring for several

minutes at -15°C the reaction was allowed to stand at -15°C for 20 hours. The reaction mixture was then filtered into a stirred mixture of 11 g of sodium bisulfite in 100 mL of water, using 200 mL of ethyl acetate to wash the filter cake. The filtrate was diluted with100 mL of water and after vigorously stirring for 1 hour was filtered. The aqueous layer was separated and discarded. The organic layer was washed with 2 X 100 mL of a 50/50 mixture of brine and 4% aqueous sodium bicarbonate. The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 4.65 g (90% yield) of the title compound as a white glass.

Step 6: [2R-[2R*,3R*(1R*),6R*,7S*,8S*,9R*,10R*]]-7-[(4-O-Benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oxobutyl)-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*),6R*,7S*,8S*,9R*,10R*]]-9-[[2-O-Acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-7-[(4-O-benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oxobutyl)-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (4.65 g, 5.3 mmol), from Step 5, was dissolved in 100 mL of methanol and kept at 25°C for 4 days. A small amount of precipitate was removed by filtration and the solvent was removed *in vacuo*. The dried residue (4.39 g) was chromatographed on 200 g of silica gel which had been preconditioned and was eluted with ethyl acetate/heptane/ammonium hydroxide (69.8:30:0.2) to give 1.57 g (35 % yield) of the title compound as a white foam.

Step 7: [2R-[2R*,3R*(1R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oxobutyl)-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*),6R*,7S*,8S*,9R*,10R*]]-7-[(4-O-Benzyloxycarbonyl-2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oxobutyl)-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one [8.2.1]tridec-12-en-5-one (1.52 g, 1.83 mmol) was dissolved in 100 mL of methanol. To the resultant solution was added 75 mg of 10% palladium on carbon. The reaction mixture was shaken at ambient temperature under 4 atmospheres of hydrogen for 1 hour. TLC

analysis on silica gel plates eluted with chloroform/methanol/concentrated ammonium hydroxide (9.5:0.5:0.2) indicated that the reaction was complete. The catalyst was removed by filtration and the filter cake was washed with 100 mL of methanol. The filtrate was concentrated under reduced pressure to give 1.267 g (99% yield) of the title compound.

Step 8: [2R-[2R*,3S*(1S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oximidobutyl)-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3R*(1R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-oxobutyl)-9-[[3,4,6-trideoxy-3-(dimethylamino))-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (1.211 g, 1.735 mmol), from Step 7, was dissolved in 82 mL of absolute ethyl alcohol. To this solution was added 601 mg (8.65 mmol) of hydroxylamine hydrochloride, followed by 725 µL (5.18 mmol) of triethylamine. The reaction mixture was heated at reflux temperature and monitored by analytical HPLC on a YMC reverse phase AQ-303 column eluted at 1 mL/min with water/acetonitrile/methanol (5:4.5:0.5) containing 6.5 g/L of ammonium acetate. After 18 hours, the reaction mixture was concentrated to a few mLs. Ethyl acetate (150 mL) and 33 mL of 8% aqueous sodium bicarbonate solution were added. The organic layer was washed with 2 X 33 mL of 8% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was carried on to the next step without purification.

Step 9: Diastereomeric mixture of [2R-[2R*,3S*(1S*,2R*),6R*,7S*,8S*,9R*,10R*]]-3-(2-amino-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one and
[2R-[2R*,3S*(1S*,2S*),6R*,7S*,8S*,9R*,10R*]]-3-(2-amino-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

[2R-[2R*,3S*(1S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-3-(1-methyl-2-

oximidobutyl)-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (997 mg), from Step 8, was dissolved in 10% ammonium hydroxide in 100 mL of methanol. To this solution was added 2.5 g of Raney nickel and the reaction mixture was shaken at ambient temperature under 4 atmospheres of hydrogen for 18 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The dry residue (895 mg) was dissolved in 120 mL of ethyl acetate and the ethyl acetate solution was washed with 3 X 33 mL of 8% aqueous sodium bicarbonate solution and 30 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give 799 mg of the title mixture as a white glass. The product was carried on to the next step without purification.

Step 10: [2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

The diastereomeric mixture of [2R-[2R*,3S*(1S*,2R*),6R*,7S*,8S*, 9R*,10R*]]-3-(2-amino-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one and [2R-[2R*,3S*(1S*,2S*),6R*,7S*, 8S*,9R*,10R*]]-3-(2-amino-1-methylbutyl)-7-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (345.1 mg) was dissolved in 9.0 mL of methanol. To this solution was added 1.0 mL of concentrated ammonium hydroxide and the resultant solution was heated at 45°C in a screw capped vial for 9 days. The solution was concentrated *in vacuo* to give 338.6 of a glass. The glass (300 mg) was dissolved in 2.0 mL of methanol and purified by preparative HPLC chromatography. The HPLC column, a D-ODS-7 (20 X 250 cm) C8 reverse phase column was eluted at 14 mL/min. The eluent was prepared by dilution of 36 g of ammonium acetate with 2.1 L of water and 1 L of acetonitrile. The methanol solution was filtered through a 45 μ nylon filter and injected onto the column in 5 batches (4 X 400 μL and 1 X 200 μL). The first peak to elute from the column (fraction A; RT=18.6 min) was collected in a flask containing 150 mL of 1 N aqueous ammonium hydroxide. The second peak to elute from the column (fraction B) was collected at 22.8 min. Each fraction was separately concentrated

in vacuo at 45°C to remove acetonitrile. 10% Aqueous sodium carbonate solution (25 mL) was added to the resulting aqueous mixture which was extracted with 5 X 20 mL of chloroform. The combined chloroform extracts were washed with a mixture of 15 mL of brine and 2 mL of concentrated ammonium hydroxide, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. Acetonitrile was added to the residue to azeotropically remove residual chloroform and water and evaporated under reduced pressure to give 65.4 mg (19% yield) of Fraction A (the title compound) and 105 mg (31% yield) of Fraction B (the 2S*-2-amino diastereomer). Fraction A: FAB MS M/Z: 699 $(M+H)^+$; IR (0.15% in CCl_4) 3565, 3480, 1650 cm^{-1}. Fraction B: FAB MS M/Z: 699 $(M+H)^+$; IR (0.15% in CCl_4) 3558, 3470, 1720 cm^{-1}.

Example 4

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (2 g, 2.8 mmol), the product of Example 1, was dissolved in 40 mL of methanol. To this solution at ambient temperature was added 1.9 g (14 mmol) of sodium acetate, followed by 390 mg (1.54 mmol) of iodine,and the resultant solution was exposed to light for 45 minutes. The iodine color was no longer visible. A second portion of iodine (390 mg, 1.54 mmol) was added and the solution again exposed to light for 1.5 hours. The reaction mixture was then poured into a separatory funnel containing 50 mL of methylene chloride and washed with a mixture of approximately 21 mL of brine and 50 mL of 5% aqueous sodium bicarbonate solution containing 100 mg of sodium thiosulfate. The aqueous layers were extracted with 5 X 25 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue (1.82 g) was chromatographed on 150 g of silica gel eluted with chloroform/methanol/ammonia (100:3:0.3) to give 865 mg (44% yield) of the title

compound; FAB MS M/Z: 701 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3438, 3353 and 1660 cm^{-1}.

In another run, the solvent used for workup was ethyl acetate instead of methylene chloride, and the product was crystallized from acetonitrile, instead of being purified by chromatography. mp 170-175°C. $[\alpha]_D$ = -29.0° (c=1.00, MeOH, 28°C). IR (CCl_4) 963, 1665, 1700 cm^{-1}. Anal Calc. for $C_{36}H_{64}N_2O_{11}$: C, 61.69; H, 9.20; N, 4.00; Found: C, 61.39; H, 9.02; N, 3.95.

Example 5

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (53 mg, 0.076 mmol), the product of Example 4, was dissolved in 3 mL of methanol. To this solution was added 25 mg of 10% palladium on carbon and 50 µL (0.82 mmol) of acetaldehyde. The reaction mixture was shaken at ambient temperature under 4 atmospheres of hydrogen for 18 hours. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was washed with 50 mL of 5% aqueous sodium bicarbonate and the aqueous mixture was extracted with 3 X 7 mL of methylene chloride. The combined organic extracts were washed with brine and concentrated *in vacuo*. The residue (43.3 mg) was combined with additional material from an identical reaction (total=200 mg) and chromatographed on a 1 X 40 cm silica gel column eluted with toluene/methanol (20:1) to give 98.6 mg of solid. The solid was dissolved in 4 mL of acetonitrile and filtered. The filtrate was concentrated *in vacuo* to give 62.8 mg of the title compound; FAB MS M/Z: 729 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3440, 3355 and 1660 cm^{-1}.

Example 6

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methyl(2-propenyl)amino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (60.9 mg, 0.087 mmol), the product of Example 4, was dissolved in 1.5 mL of acetonitrile. To this solution was added 25 µL (0.289 mmol) of cold allyl bromide and the reaction mixture was stirred at ambient temperature for approximately 8 hours. The reaction mixture was diluted with 50 mL of 5% aqueous sodium bicarbonate solution and was extracted with 3 X 15 mL of methylene chloride. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a glassy solid. The glass (54.8 mg) was purified by chromatography on silica gel eluted with toluene/methanol (20:1) to give 19.6 mg (31% yield) of the title compound; FAB MS M/Z: 741 $(M+H)^+$.

Example 7

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethyl(2-propenyl)ammonium)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabi-cyclo[10.2.1]pentadec-14-en-7-one bromide

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (200 mg, 0.28 mmol), the product of Example 1, was dissolved in 3 mL of acetonitrile. To this solution was added 80 µL (0.924 mmol) of allyl bromide and the reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was concentrated *in vacuo*. The residue was triturated with ethyl acetate. The solid phase was dried *in vacuo* to

give 160 mg (68% yield) of the title compound; FAB MS M/Z: 755 (M^+-Br); IR (KBr) 1703, 1650 cm^{-1}.

Example 8

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one 13-O,14-O-carbonate

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (177 mg, 0.248 mmol), the product of Example 1, was dissolved in 2 mL of toluene/THF (1:1). To this solution was added 0.37 g (2.68 mmol) of potassium carbonate, followed by 0.78 g (8.86 mmol) of ethylene carbonate (commercially available from Aldrich Chemical Company). The reaction mixture was heated at reflux temperature for 3 hours, cooled to ambient temperature, diluted with 50 mL of 5% aqueous sodium bicarbonate and extracted with 3 X 25 mL of toluene. The organic phase was washed with 50 mL of brine and concentrated *in vacuo* to an oil which solidified upon standing at ambient temperature. The residue was chromatographed on silica gel eluted with chloroform/acetonitrile/methanol/ammonia (10:2.5:0.25:0.03) to give 66.7 mg (19% yield) of the title compound; DCI NH_3 MS M/Z: 741 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3440, 3358, 1805 and 1678 cm^{-1}.

Example 9

[1R-(1R*2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*,14S*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadecan-7-one

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-

aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (210.7 mg, 0.295 mmol), the product of example 1, was dissolved in 20 mL of glacial acetic acid. To the resultant solution was added 40 µL (2.157 equivalents) of difluoroacetic acid (DFA) and 210 mg of platinum oxide. The reaction mixture was shaken at ambient temperature under 4 atmospheres of hydrogen for 4 hours. Ammonium acetate (160 mg) was added and the resultant mixture was shaken for 1.0 minutes. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was diluted with 50 mL of chloroform. A mixture of 50 mL of brine and 10 mL of concentrated ammonium hydroxide was added. The chloroform layer was separated and the aqueous layer was extracted with 30 mL of chloroform. The combined chloroform layers were washed with a mixture 40 mL of brine and 5 mL of concentrated ammonium hydroxide. The chloroform solution was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was evaporated from acetonitrile to remove all of the chloroform and dried under vacuum to give 230.4 mg of a white glass. The title compound was separated from the other components of the crude product by preparative HPLC on a reverse phase YMC D-ODS-7 column (20 X 250 mm) eluted at 10 mL/min with 40% methanol in water containing 10 g/L of triethylamine hydrochloride, 0.1 mL/L of glacial acetic acid and 30 mL/L of ethylene glycol. The crude product (the white glass) was dissolved in 2.0 mL of methanol and the solution was filtered through a 0.4 µ nylon filter. The methanol solution was injected onto the HPLC column in 6 portions totalling 1.755 mL. The peak collected at 14.7 min was combined from each run and concentrated to less than one half of the collected volume using a rotary evaporator and water bath heated to 45°C. The concentrate was diluted with an equal volume of brine and then made basic (pH 10) with 20 mL of 10% aqueous sodium carbonate solution. The product was extracted with 4 X 25 mL of chloroform. The combined extracts were washed with 30 mL of water, dried over anhydrous sodium sulfate, filtered and concentrated to dryness under reduced pressure. After vacuum drying, the residue was dissolved in 2 mL of acetonitrile and treated with 50 mg of sodium bicarbonate. After the mixture was stirred for 15 min, it was filtered and the filtrate was concentrated to dryness under a stream of nitrogen. The title compound (30.3 mg) was obtained after vacuum drying; FAB MS M/Z: 717 $(M+H)^+$; IR (0.15% in CCl_4) 3560. 3470, 3440, 3345 and 1660 cm^{-1}.

Example 10

Reaction of [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one with Aqueous Acetic Acid

To [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(di-methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (515 mg, 0.72 mmol), the product of example 1, suspended in 20 mL of water, was added 20 mL of glacial acetic acid. The reaction mixture was stirred at ambient temperature for approximately 4 hours and then poured into 300 mL of water. The solution was made basic (pH 8-9) by adding 5% sodium bicarbonate solution and ammonium hydroxide and gently swirling. The aqueous solution was poured into a separatory funnel containing methylene chloride and the methylene chloride layer was separated. The aqueous layer was extracted with 3 X 100 mL of methylene chloride. The combined methylene chloride extracts were concentrated under reduced pressure to give 300 mg of the acid degradation products. One of those products was identified as the corresponding anhydro compound, [1R-(1R*, 2R*, 3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*,14R*)]-9-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethyl-amino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15,16-dioxatricyclo[10.2.1.$1^{1,4}$] pentadecan-7-one. A crude sample of the anhydro compound (540 mg) was chromatographed on silica gel (approximately 100 g) equilibrated with chloroform/acetonitrile/methanol/ammonia (10:3:0.4:0.03) and eluted with chloroform/acetonitrile/methanol/ammonia (10:3:0.6:0.006) to give 100 mg of the anhydro compound. FAB MS M/Z: 715 $(M+H)^+$; IR (0.15% in CCl_4) 3460, 3435, 3330 and 1645 cm^{-1}; ^{13}C NMR (DMSO-d6) C9 at 114.3 ppm. $[\alpha]_D^{23}$ = -11.8° (c 1.00; MeOH). A sample was crystallized from acetonitrile, m.p. 178-182°C.

Example 11

Reaction of [2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one with Aqueous Hydrochloric Acid

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one (874 mg, 1.22 mmol), the product of example 1, was dissolved in acetonitrile and the solution was concentrated down to a foam under reduced pressure. Water (50 mL) was added to the foam while the sides of the flask were scraped. A solution of 2 mL of 1 N aqueous hydrochloric acid in 100 mL of water was prepared and 39.33 mL of this solution was added portionwise to the aqueous erythromycin A lactam enol ether. After the addition was complete the pH of the resultant solution was 3. As sample dissolved it was necessary to adjust the pH by the addition of 1 N aqueous hydrochloric acid in order to maintain the pH at approximately 2.5. After stirring for 90 minutes the reaction mixture was quenched by pouring the acidic solution into a separatory funnel with 100 mL of 5% aqueous sodium bicarbonate solution and 3 mL of concentrated ammonium hydroxide. The aqueous layer was extracted with 3 X 50 mL of methylene chloride. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Silica gel (approximately 100 g) was slurried with acetonitrile/ammonia (10:0.5) and poured into a column. The column was equilibrated with 2 L of chloroform/acetonitrile/methanol/ ammonia (10:3:0.5:0.05). The residue was loaded on the column and the column was eluted with chloroform/acetonitrile/methanol/ammonia (10:0.3:0.5:0.05) to give 160 mg of [3R-(3R*,4S*,5S*,6R*,7R*,9S*,11R*,12R*, 13R*,14R*)]-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]aza-cyclotetradecane-2,10-dione (erythromycin A lactam"). FAB MS M/Z: 733 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3430, 1675 and 1655 cm^{-1}; ^{13}C NMR (DMSO-d6) C9 at

217.2 and 107.6 (mixture of ketone and 9,12-hemiacetal). $[\alpha]_D^{23}$ = -52.9° (c 1.00; MeOH).

Example 12

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

A solution of 15% methylamine in methanol was prepared by adding 15 mL of liquid methylamine in 85 mL of methanol cooled to 0°C in an ice bath. [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8, 10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylohexo-pyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (441.6 mg, 0.6327 mmol), from Step 4 of Example 1, was dissolved in 10 mL of the methylamine solution in a 20 mL heavy-walled reaction tube. The reaction tube was sealed with a teflon screw cap and "O" ring and then the tube was heated at 100°C in an oil bath for 5 days. The reaction mixture was sampled and analyzed using the HPLC system described in Step 3 of Example 1 A. According to HPLC analysis, the epoxide starting material was consumed. The crude reaction material was diluted with 100 mL of 8% aqueous sodium bicarbonate solution and extracted with 3 X 25 mL of chloroform. The chloroform extract was washed with 50 mL of a 1:1 solution of 8% aqueous sodium bicarbonate and brine. The chloroform solution was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in 30 mL of acetonitrile and the solvent removed *in vacuo* to give a dark yellow residue. The residue (430 mg) was chromatographed on 50 g of silica gel which had been equilibrated with chloroform/acetonitrile/ methanol/ammonium hydroxide (87.8:10:2:0.2 v/v/v/v), eluting at 2.1 mL/min with the same solvent used for equilibration followed, after collecting sixty five 15 mL fractions, by chloroform/acetonitrile/methanol/ammonium hydroxide (83.6:10:6:0.4 v/v/v/v) to give 275.2 mg (60% yield) of the title compound; DCI/NH_3 MS M/Z: 729 $(M+H)^+$; IR (0.15% in CCl_4) 3560, 3510, 3460, 1700 and 1625 cm^{-1}. $[a]_D$ 22°C = -58.7° (c 1.00; MeOH).

Example 13

Alternate preparation of [2R-[2R*,3R*(1R*,2R*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-dihydroxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8,2,1]tridec-12-en-5-one

Erythromycin A (30.01 g, 40.89 mmol) was suspended in 200 mL of acetonitrile. To the stirred suspension was added 10.541 g (81.751 mmol) of dichloroacetic acid in 100 mL of acetonitrile over a 20 minute period; the erythromycin dissolved after addition of about half the volume. The reaction was stirred for 2.5 hours at 23°C giving the enol ether. To the solution containing the enol ether intermediate was added over a 30 minute period a solution of 16.951 g (122.65 mmol) of potassium carbonate dissolved in 300 mL of 1:1 (v/v) methanol:water. The mixture was then refluxed for 1.5 hours, cooled to room temperature and concentrated *in vacuo* to leave a white residue. The residue was dissolved in a mixture of 200 mL of chloroform, 200 mL of 8% sodium bicarbonate solution and 100 mL of saturated brine. The organic layer was then separated, the aqueous layer extracted with chloroform and the organic layers combined. This solution was washed with a mixture of sodium bicarbonate solution and saturated brine, dried over sodium sulfate, filtered and concentrated to dryness. The residue was dissolved in 100 mL of acetonitrile and evaporated in vacuo to give 28.67 g of crude product as a foam. The material was crystallized from acetonitrile to afford 18.717 g of the title product. A second extraction was performed, and the total yield for the reaction found to be 69%.

Example 14

[2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8,2,1]tridec-12-en-5-one

Step 1. [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

A 3.001 g (4.300 mmol)) sample of [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,-10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one (the product of Example 1A, step 2 above) was dissolved in 40 mL of methylene chloride, and 1.2 mL of triethyl amine and 0.81 mL of acetic anhydride were added. The reaction was allowed to proceed for 24 hours, whereupon the solvent was removed under vacuum and the residue dissolved in 100 mL of ethyl acetate. The ethyl acetate solution was washed with 8% $NaHCO_3$, 5% NaH_2PO_4, H_2O and 8% $NaHCO_3$ solutions, then dried over sodium sulfate, filtered and taken to dryness. Exhaustive drying yielded 3.175 g of the title product. This material was taken to the next step without further purification.

Step 2. [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-4-O-imidazolylthiocarbonyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

A 3.109 g sample of the product of Step 1 above, 2.064 g (16.894 mmol) of DMAP and 2.260 g (12.681 mmol) of 1,1'-thiocarbonyldiimidazole (Aldrich) were dissolved in 40 mL of methylene chloride, and the reaction allowed to proceed at 25°C for 18 hours. To the reaction mixture was then added 1.15 mL of concentrated NH_4OH, and the reaction stirred at room temperature.for 45 minutes. Next was added 100 mL of 0.5 M acetate buffer, followed by 2 mL of acetic acid to adjust the pH to 6.0, and the mixture stirred for 2 hours.. Additional solvent was added, and the organic phase separated. After washing first with acetate buffer (pH 4.7), and then with 8% $NaHCO_3$, the solution was dried over sodium sulfate, filtered and taken to dryness to yield 3.357 g of the title compound.

Step 3. [2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one

A mixture of 3.319 g (3.905 mmol) of the product of step 2 above and 0.128 g (0.779 mmol) of AIBN (2,2'-azobis(2-methylpropionitrile) was dissolved in 60 mL of dry toluene. To this was added 2.2 mL (6.98 mmol) of tri-*n*-butyl tin hydride, and the mixture degassed and held under N_2 before heating in an oil bath at 100°C for 1 hour. The mixture was concentrated to a syrup, then dissolved in 100 mL of $CHCl_3$. This solution was washed with acetate buffer (pH 4.7), then with 8% aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and taken to dryness to yield 5.653 g of a residue. The residue was dissolved in 200 mL of acetonitrile and washed 3 times with 50 mL portions of hexane. The acetonitrile layer was concentrated to dryness to afford 2.69 g of the title product.

Example 15

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

A 508 mg sample of the product of Example 14 was placed in a 20 mL pressure tube. The sample was dissolved in 10 mL of 15% NH_3 in methanol, flushed with N_2, sealed and heated at 100°C in an oil bath for 4 days. The contents of the tube were taken to dryness, and the crude product purified by preparative chromatography on silica gel, eluting with 0.2:2:10:100 NH_4OH:methanol:acetonitrile:$CHCl_3$. The solvent was removed from the fractions containing the product to afford 228 mg of the title compound as a glass. MS M/Z 699 (M+H). IR (CCl_4): 3520b, 3480b, 3440sh, 3355sh, 1700w, 1662s. $[\alpha]_D$ = -33.6° (c=0.50, MeOH, 24°C). Anal Calc. for $C_{37}H_{66}N_2O_{10}$: C, 63.58; H, 9.52; N, 4.01; Found: C, 63.15; H, 9.48; N, 3.98.

Example 16

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

A 607.2 mg sample of the product of Example 14 was placed in a 20 mL pressure tube, and 10 mL of 15% methylamine in methanol was added. The tube was flushed with N_2, sealed and heated at 100°C in an oil bath for 4 days. The tube was opened, and the solvent removed to yield 634 mg of crude product. This material was purified by chromatography on silica gel, eluting with 0.2:2:10:100 NH_4OH:methanol:acetonitrile:$CHCl_3$. The solvent was removed from the fractions containing the product to afford 302.4 mg of the title compound as a glass. $[\alpha]_D$ = -55.0° (c=1.00, MeOH, 29°C). IR (CCl_4): 3510b, 3460b, 1700w, 1622s cm^{-1}. Anal Calc. for $C_{38}H_{68}N_2O_{10}$: C, 64.02; H, 9.61; N, 3.93; Found: C, 64.02; H, 9.67; N, 3.92.

Example 17

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*n*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

To a heavy-walled flask (Parr Instrument Co.) were added 311 mg of the product of Example 4, 30 mL of methanol, 120 mg of 10% Pd/C and 0.30 mL of butyraldehyde. The flask was charged with 4 atm of hydrogen and shaken for 16 hours. The catalyst was removed by filtration, and the solvent was removed under vacuum. The residue was dissolved in acetonitrile and taken to dryness twice to give 340 mg of crude product. The crude product was purified by reverse phase HPLC, eluting with 40:60 acetonitrile:water containing 10 g/L of ammonium acetate. The eluent fractions were concentrated to half their volume and were made alkaline by the addition of 1 N NaOH in small portions. The product was extracted into chloroform which was washed with 8% aqueous $NaHCO_3$, dried over sodium sulfate, filtered and concentrated. The residue was dissolved in acetonitrile

which was then removed under vacuum to yield 170.6 mg of the title product as a glass. MS M/Z 757 (M+H). [α]D = -32.9° (c=1.00, methanol, 28°C). IR (CCl_4): 3560, 3520, 3440, 1702, 1660 cm^{-1}. Anal Calc. for $C_{40}H_{72}N_2O_{11}$: C, 63.46; H, 9.59; N, 3.70; Found: C, 62.95; H, 9.48; N, 3.63.

Example 18

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*n*-propylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

By a procedure similar to that described in Example 17, 382 mg of the product of Example 4 was reacted with propionaldehyde instead of butyraldehyde, to afford 196.2 mg of the title compound as a white glass. MS M/Z 743 (M+H). [α]D = -32.8° (c=1.00, methanol, 28°C). Anal Calc. for $C_{39}H_{70}N_2O_{11}$: C, 63.05; H, 9.50; N, 3.79; Found: C, 63.05; H, 9.50; N, 3.79.

Example 19

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-propylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

In a 20 mL pressure tube were placed 200 mg of the product of Example 4, 0.5 mL of diisopropylethylamine, 1.0 mL of 2-iodopropane and 2.0 mL of acetonitrile. The tube was flushed with N_2, sealed and heated at 70°C in an oil bath. For workup, the products of two such runs were combined. The solvents were remove, and the residue was dissolved in a mixture of 30 mL ethyl acetate, 20 mL of 8% aqueous $NaHCO_3$ and 100 mg of sodlium thiosulfate. The organic layer was washed, dried and filtered, to give 354 mg of crude product. The crude product was purified by HPLC by a procedure similar to that described in Example 19 to

afford 196.2 mg of the title compound as a white glass. MS M/Z 781 (M+H). [α]D = -32.8° (c=1.00, methanol, 27°C). Anal Calc. for $C_{39}H_{70}N_2O_{11}$: C, 63.05; H, 9.50; N, 3.79; Found: C, 62.54; H, 9.50; N, 3.77.

Example 20

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one

By a procedure similar to that described in Example 19, 400 mg of the product of Example 4 were reacted with 2-iodobutane instead of 2-iodopropane to afford, after purification by HPLC, two samples (the N-(S)-2-butyl and N-(R)-2-butyl isomers).

21a. (S-isomer): 134 mg; MS M/Z 757 (M+H). [α]D = -30.2° (c=0.5, methanol, 27°C). IR 3560, 3440, 3350, 1700, 1658 cm^{-1}.

21b. (R-isomer): 112.5 mg; MS M/Z 757 (M+H). $[\alpha]_D$ = -36.4° (c=0.5, methanol, 27°C). IR 3560, 3440, 3350, 1700, 1659 cm^{-1}.

Example 21

In Vitro Assay of Gastric Prokinetic Activity

The compounds of the present invention were tested *in vitro* for their ability to induce contraction of smooth muscle strips isolated from rabbit small intestine using the following procedure.

Rabbits were sacrificed and 15 cm of duodenum was rapidly removed and placed in ice-cold modified Ringers solution (120 mM sodium chloride, 25 mM sodium bicarbonate, 4.7 mM potassium chloride, 1.25 mM calcium chloride, 1.20 mM magnesium sulfate and 5.6 mM glucose). The longitudinal muscle layer was separated from the circular muscle by blunt dissection and cut into strips of 10 X 20 mm. Double-folded strips were vertically suspended between two hooks in 10 mL tissue baths with a mechanical preload of 1 g. The upper hook was connected to an isotonic force transducer, and its displacement was recorded on a Grass polygraph. The tissue baths contained modified Ringers solution at 37°C and were

continuously gassed with 95% oxygen/5% carbon dioxide in order to maintain the pH at 7.5.

After a stabilization period of at least 60 minutes, a contractility dose-response series was performed by adding increasing final concentrations of methacholine (10^{-7} M, 10^{-6} M and 10^{-5} M) in volumes of 100 µL. The bath solutions were replaced at least three times between doses.

After the methacholine dose-response series was completed, a test compound dose response curve was initiated by the same procedure used for the methacholine dose-response series, with at least five concentrations of test compound within the range of 10^{-10} M to 10^{-4} M. The tissues were washed repeatedly between doses, and the studies were completed by recording the contractile response to 10^{-5} M methacholine to ascertain integrity of the muscle preparation. Contractile responses were expressed as percent of maximal contraction. The concentration of test compound which produces half of the maximal contraction (ED_{50} value) and the negative logarithm of the ED_{50} value (pED_{50}) were estimated from the dose-response curves. The pED_{50} values are shown in Table 1 in comparison to erythromycin A which is a known gastrointestinal prokinetic agent. From these data it is evident that the compounds of the present invention are potent prokinetic agents.

Table 1

In Vitro Rabbit Duodenal Smooth Muscle Contraction Assay

Example Number	pED_{50} (-log M)	Relative Potency
1	7.10	18.0
3	7.50	45.0
4	6.50	5.0
5	7.10	18.0
7	6.60	5.6
8	6.30	3.0
9	6.25	2.5
10	6.10	1.8
12	7.22	23.4
15	8.27	263
16	8.50	447

17	5.67	0.66
18	6.00	1.41
19	7.63	60.3
20 (S)	8.40	355
20 (R)	9.27	2630
erythromycin A	5.85	1.0

Example 22

Gastrointestinal Prokinetic Activity: *In Vivo* Assay in Anesthetized Dogs

The compounds of the present invention were tested *in vivo* for their ability to induce gastrointestinal motility using the following procedure: Adult female beagle dogs, food deprived for 16 - 20 hours and weighing between 7.0 and 12.0 kg, were anesthetized with 30 mg/kg of sodium pentobarbital given intravenously. Anesthesia was maintained during the experimental procedure by continuous intravenous infusion of 5 mg/kg Nembutal in 0.9% saline. After tracheal intubation, the animals were mechanically respired with a Harvard positive pressure respiratory pump. Rectal temperature was maintained at 37°C by a heated animal table. A polyethylene catheter was inserted into the right femoral artery to record blood pressure and heart rate using a Steatham P23 pressure transducer. Polyethylene catheters were also introduced into the right femoral vein for infusion of anesthetic and the left femoral vein for drug administration and blood samples. The abdomen was opened by a midline incision immediately below the xiphoid process extending to 2 cm below the umbilicus.

Five strain-gauge transducers were used to monitor contractile activity of the circular muscle layer of the stomach or intestine. Each was calibrated to give a 60% full scale deflection when supporting a 100 g weight between two planar surfaces. However, due to variability in transducer response, output when applied to the circular muscle layer was observed to vary despite the first stage of calibration. Therefore, final sensitivity adjustments were subsequently made with transducers sewn in place to yield comparable deflections of paired transducers. Two transducers were sutured to the serosal surface of the antrum of the stomach. The first was approximately 5 cm proximal to the pylorus and the second 1 cm proximal to the first. Two transducers were also sutured to the duodenum; they were approximately 12 cm distal to the pylorus and about 1 cm apart. Only one

transducer was sutured to the jejunum, approximately 10 cm from the ligament of Treitz, and was not pair calibrated. Two transducers were used in both the stomach and duodenum to minimize variability. After application of the transducers, the abdominal wound was closed and gastrointestinal motility patterns were allowed to stabilize for from 45 to 90 minutes before drug administration.

Motility and blood pressure were recorded by a Grass Model 7 oscillograph. The records were manually analyzed by a scoring system which included both magnitude and duration of muscular contractions. The manual scoring system consisted of pulse-height measurement by counting recorded contractile waves in relation to five selected amplitudes (7, 17, 34, 68, 136, >136 g). A transparent guide was used to facilitate scoring. A minimal pulse-height score was assigned for every contraction between each of these levels (a score of 0.5 for all contractions between 7 and 17 g, a score of 1.0 for contractions between 17 and 34 g, a score of 2.0 for contractions between 34 and 68 g, a score of 4.0 for contractions between 68 and 136 g and a score of 8.0 for contractions over 136 g). Scores were computed for the 60 minute period following drug administration. Mean scores were computed for the two transducers in both stomach and duodenum. Drugs were administered for either 2 or 3 periods, each period consisting of 90 minutes. In period 1, the test compound was typically administered and motility responses recorded for 60 minutes. In period 2, erythromycin A lactobionate was then administered to establish an internal control for each animal studied. All compounds for one experiment were given at the same dose, usually 4.0 mg/kg.

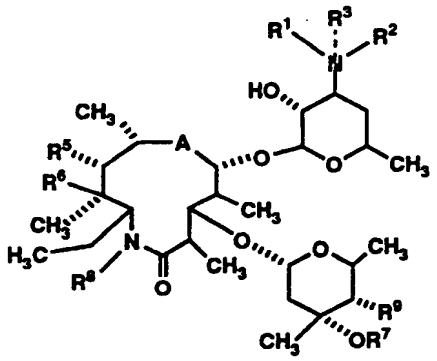
Several experiments were done with erythromycin A lactobionate alone. Erythromycin was administered in both periods and the data analyzed in the standard manner. Due to dose-dependent tachyphylaxis, a motility response induced by erythromycin in period 1 resulted in reduced erythromycin response in period 2. Test compounds should ideally be investigated by both prior and subsequent administration with respect to erythromycin dosing to minimize tachyphylactic bias. For initial screening, however, the standard protocol was test compound (period 1) followed by erythromycin (period 2).

The final expression of results was a ratio between the motility scoring for the test compound (period 1) and erythromycin A lactobionate (period 2). For stomach, duodenum and jejunum, the motility score in response to the test compound was divided by the motility score for erythromycin. From these three ratios, an arithmetic mean ratio for "overall motility index" was calculated in which contributions from the

three tissue areas measured were weighted equally. The compound of Example 1, when tested *in vivo* as described above, exhibited a motility index of 19.9 compared to erythromycin A, which was assigned a motility index of 1, demonstrating that the compounds of the invention exhibit potent gastrointestinal prokinetic activity *in vivo*.

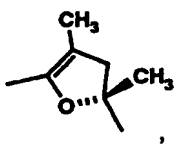
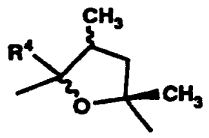
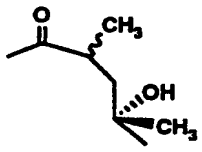
We claim:

1. A compound having the formula



or a pharmaceutically acceptable salt thereof, wherein the dotted line is an optional bond;

A is selected from the group consisting of


,  and  ;

R^1 and R^2 are independently be selected from the group consisting of hydrogen, loweralkyl, halo-substituted loweralkyl, cyano-substituted loweralkyl, hydroxy-substituted loweralkyl, loweralkenyl, loweralkynyl, lower cycloalkyl, lower cycloalkylmethyl and benzyl;

R^3 is absent or is selected from the group consisting of loweralkyl, loweralkenyl, loweralkynyl and benzyl and accompanied by a pharmaceutically acceptable counterion so as to form a quaternary ammonium salt;

R^4 is hydrogen or, taken together with R^6, forms an ether bridge;

R^5 is selected from the group consisting of -OH and $-OR^9$, wherein R^9 is selected from loweralkyl, loweralkanoyl and $-S(O)_2CH_3$, or, taken together with R^6 and the carbons to which they are attached, forms a cyclic carbonate;

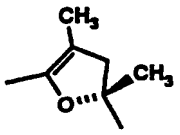
R^6 is selected from the group consisting of hydrogen, -OH and $-OR^{10}$ wherein R^{10} is selected from loweralkyl, loweralkanoyl and $-S(O)_2CH_3$; or, taken together

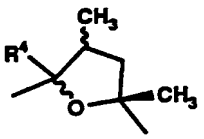
with R^4, forms an ether bridge; or, taken together with R^5 and the carbons to which they are attached, forms a cyclic carbonate;

R^7 is selected from the group consisting of hydrogen and methyl;

R^8 is selected from the group consisting of hydrogen and loweralkyl; and

R^9 is selected from the group consisting of hydrogen and hydroxy.

2. A compound according to Claim 1 wherein A is  .

3. A compound according to Claim 1 wherein A is  .

4. A compound according to Claim 3 wherein R^5 and R^6, together with the carbon atoms to which they are attached, form a cyclic carbonate.

5. A compound according to Claim 3 wherein R^4 and R^6 taken together form an ether linkage.

6. A compound according to Claim 1 wherein the compound is selected from the group consisting of

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin A lactam enol ether");

[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin B lactam enol ether");

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(methyl(2-propenyl)amino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethyl(2-propenyl)ammonium)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabi-cyclo[10.2.1]pentadec-14-en-7-one bromide;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one 13-O,14-O-carbonate;

[1R-(1R*2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*,14S*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadecan-7-one;

[1R-(1R*, 2R*, 3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*,14R*)]-9-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15,16-dioxatricyclo[10.2.1.$1^{1,4}$] pentadecan-7-one;

[3R-(3R*,4S*,5S*,6R*,7R*,9R*,11R*,12R*,13R*,14R*)]-4-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]azacyclotetradecane-2,10-dione ("erythromycin A lactam");

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin C lactam enol ether");

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one ("erythromycin D lactam enol ether");

[2R-(2R*,3S*,4S*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3-hydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(ethylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-[2R*,3R*(1R*,2S*),6R*,7S*,8S*,9R*,10R*]]-7-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-3-(1,2-epoxy-1-methylbutyl)-2,6,8,10,12-pentamethyl-9-[[2-O-acetyl-3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-4,13-dioxabicyclo[8.2.1]tridec-12-en-5-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,4,6-Trideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*n*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

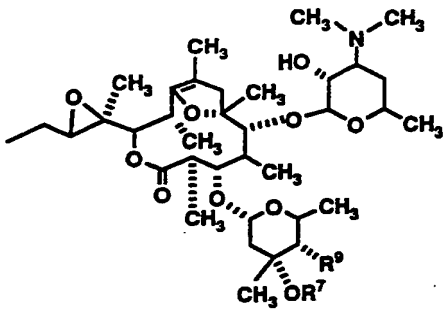
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*n*-propylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-propylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one; and

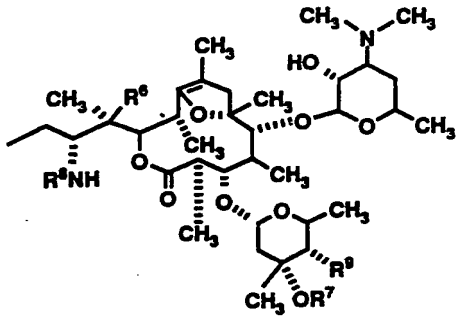
[2R-(2R*,3R*,4R*,5R*,8R*,9S*,10S*,11R*,12R*)]-9-[(2,6-Dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-5-ethyl-3,4-dihydroxy-2,4,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(*i*-butylmethylamino)-β-D-xylo-hexopyranosyl]oxy]-6-aza-15-oxabicyclo[10.2.1]pentadec-14-en-7-one;

and pharmaceutically acceptable salts thereof.

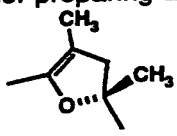
7. An intermediate useful in the preparation of a compound according to Claim 1 having a formula selected from the group consisting of

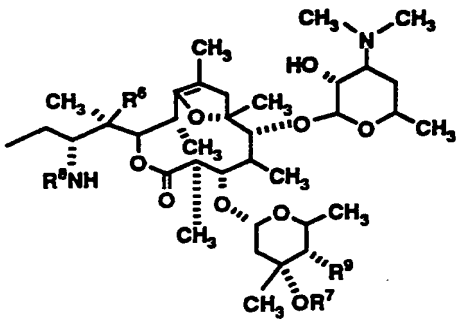


and

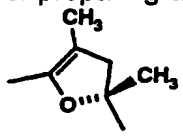


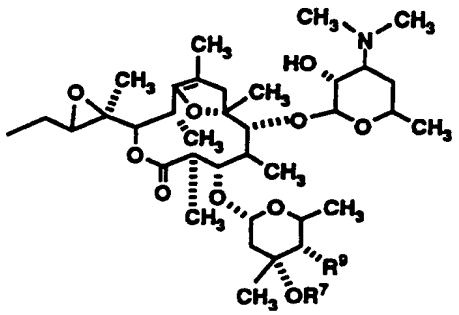
wherein R^6 is selected from the group consisting of hydrogen and -OH;
R^7 is selected from the group consisting of hydrogen and methyl;
R^8 is selected from the group consisting of hydrogen and loweralkyl; and
R^9 is selected from the group consisting of hydrogen and hydroxy.

8. A process for preparing a compound according to Claim 1 wherein A is a group of the formula  , comprising the step of treating an amine alcohol having the formula



with a suitable base under conditions sufficient to induce cyclization to a lactam.

9. A process for preparing a compound according to Claim 1 wherein A is a group of the formula  and R^6 is -OH, comprising the step of treating an epoxide having the formula



with an amine under conditions sufficient to induce epoxide opening and spontaneous cyclization to a lactam.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

11. A method for enhancing gastrointestinal motility in humans and other mammals in need of such treatment comprising administering a thereapeutically effective amount of a compound according to Claim 1.

12. A method of facilitating the placement of diagnostic and therapeutic instrumentation into the proximal small intestine of a human or other mammal comprising administering to such human or mammal a compound according to Claim 1 in an amount effective for enhancing gastrointestinal motility.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/02590

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/70; C07H 17/08
US CL : 514/28, 29; 536/7.1, 7.2, 7.4

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
U.S.	514/28, 29; 536/7.1, 7.2, 7.4

Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched[5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category*	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]
A	US, A, 4,512,982 (Hauske et al) 23 April 1985, see column 2, lines 1-35.	1-6 and 10-12.
A	US, A, 4,920,102 (Gidda et al) 24 April 1990, see column 1, lines 1-55.	7 and 11-12.
A	US, A, 4,958,010 (Kadow et al) 18 September 1990, see column 7, lines 29-68.	8-9.
A,E	US, A, 5,106,961 (Kirst et al) 21 April 1992, see column 2 lines 1-50.	7.

* Special categories of cited documents:[16]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2]	Date of Mailing of this International Search Report[2]
29 JUNE 1992	07 JUL 1992
International Searching Authority[1]	**Signature of Authorized Officer[20]**
ISA/US	ELLI PESELEV

Form PCT/ISA/210 (second sheet)(May 1986) &

特　許　協　力　条　約

PCT

国際予備審査報告

（法第１２条、法施行規則第56条）
〔ＰＣＴ３６条及びＰＣＴ規則70〕

出願人又は代理人の書類記号	今後の手続きについては、国際予備審査報告の送付通知（様式ＰＣＴ／ＩＰＥＡ／４１６）を参照すること。	
国際出願番号 ＰＣＴ／ＪＰ００／０５５０３	国際出願日 （日.月.年） １７．０８．００	優先日 （日.月.年）
国際特許分類（ＩＰＣ） Int.Cl' C07H17/08 // A61K31/7048, A61P11/00, 29/00		
出願人（氏名又は名称） 社団法人北里研究所		

1．　国際予備審査機関が作成したこの国際予備審査報告を法施行規則第57条（ＰＣＴ３６条）の規定に従い送付する。

2．　この国際予備審査報告は、この表紙を含めて全部で 4 ページからなる。

☐ この国際予備審査報告には、附属書類、つまり補正されて、この報告の基礎とされた及び／又はこの国際予備審査機関に対してした訂正を含む明細書、請求の範囲及び／又は図面も添付されている。
（ＰＣＴ規則70.16及びＰＣＴ実施細則第６０７号参照）
この附属書類は、全部で ＿＿＿＿＿＿ ページである。

3．　この国際予備審査報告は、次の内容を含む。

I ☒ 国際予備審査報告の基礎

II ☐ 優先権

III ☐ 新規性、進歩性又は産業上の利用可能性についての国際予備審査報告の不作成

IV ☐ 発明の単一性の欠如

V ☒ ＰＣＴ３５条(2)に規定する新規性、進歩性又は産業上の利用可能性についての見解、それを裏付けるための文献及び説明

VI ☐ ある種の引用文献

VII ☐ 国際出願の不備

VIII ☐ 国際出願に対する意見

国際予備審査の請求書を受理した日 ０４．０９．００	国際予備審査報告を作成した日 ２２．０５．０１	
名称及びあて先 日本国特許庁（ＩＰＥＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	特許庁審査官（権限のある職員） 森井　隆信	４Ｃ　９４５５
	電話番号 ０３－３５８１－１１０１　内線　３４５１	

様式ＰＣＴ／ＩＰＥＡ／４０９（表紙）（１９９８年７月）

国際予備審査報告 [redacted]

国際出願番号 PCT/[redacted]0/05503

I. 国際予備審査報告の基礎

1. この国際予備審査報告は下記の出願書類に基づいて作成された。（法第６条（ＰＣＴ１４条）の規定に基づく命令に応答するために提出された差し替え用紙は、この報告書において「出願時」とし、本報告書には添付しない。ＰＣＴ規則70.16, 70.17）

[X] 出願時の国際出願書類

[ ] 明細書 第 _____ ページ、 出願時に提出されたもの
明細書 第 _____ ページ、 国際予備審査の請求書と共に提出されたもの
明細書 第 _____ ページ、 _____ 付の書簡と共に提出されたもの

[ ] 請求の範囲 第 _____ 項、 出願時に提出されたもの
請求の範囲 第 _____ 項、 ＰＣＴ１９条の規定に基づき補正されたもの
請求の範囲 第 _____ 項、 国際予備審査の請求書と共に提出されたもの
請求の範囲 第 _____ 項、 _____ 付の書簡と共に提出されたもの

[ ] 図面 第 _____ ページ／図、 出願時に提出されたもの
図面 第 _____ ページ／図、 国際予備審査の請求書と共に提出されたもの
図面 第 _____ ページ／図、 _____ 付の書簡と共に提出されたもの

[ ] 明細書の配列表の部分 第 _____ ページ、 出願時に提出されたもの
明細書の配列表の部分 第 _____ ページ、 国際予備審査の請求書と共に提出されたもの
明細書の配列表の部分 第 _____ ページ、 _____ 付の書簡と共に提出されたもの

2. 上記の出願書類の言語は、下記に示す場合を除くほか、この国際出願の言語である。

上記の書類は、下記の言語である _____ 語である。

[ ] 国際調査のために提出されたＰＣＴ規則23.1(b)にいう翻訳文の言語
[ ] ＰＣＴ規則48.3(b)にいう国際公開の言語
[ ] 国際予備審査のために提出されたＰＣＴ規則55.2または55.3にいう翻訳文の言語

3. この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際予備審査報告を行った。

[ ] この国際出願に含まれる書面による配列表
[ ] この国際出願と共に提出されたフレキシブルディスクによる配列表
[ ] 出願後に、この国際予備審査（または調査）機関に提出された書面による配列表
[ ] 出願後に、この国際予備審査（または調査）機関に提出されたフレキシブルディスクによる配列表
[ ] 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった
[ ] 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

4. 補正により、下記の書類が削除された。
[ ] 明細書 第 _____ ページ
[ ] 請求の範囲 第 _____ 項
[ ] 図面 図面の第 _____ ページ／図

5. [ ] この国際予備審査報告は、補充欄に示したように、補正が出願時における開示の範囲を越えてされたものと認められるので、その補正がされなかったものとして作成した。（ＰＣＴ規則70.2(c) この補正を含む差し替え用紙は上記１．における判断の際に考慮しなければならず、本報告に添付する。）

国際予備審査報告

国際出願番号　ＰＣＴ／ＪＰ００／０５５０３

Ⅴ．　新規性、進歩性又は産業上の利用可能性についての法第１２条（ＰＣＴ３５条(2)）に定める見解、それを裏付ける文献及び説明

１．　見解

新規性（N）	請求の範囲	3, 4, 5-20, 22, 23, 27-34, 36, 40-52	有
	請求の範囲	1, 2, 21, 24-26, 35, 37-39	無
進歩性（ＩＳ）	請求の範囲		有
	請求の範囲	1-52	無
産業上の利用可能性（ＩＡ）	請求の範囲	1-52	有
	請求の範囲		無

２．　文献及び説明（ＰＣＴ規則70.7）

文献１：EP, 838469, A (Solvay Pharmaceuticals G.m.b.H.)
29.4月.1998(29.04.98)
文献２：EP, 550895, A1 (Kali-Chemie Pharma GmbH) 14.7月.1993(14.07.93)
文献３：EP, 382472, A2 (Lilly, Eli, and Co.) 16.8月.1990(16.08.90)
文献４：EP, 296717, A2 (Lilly, Eli, and Co.) 28.12月.1988(28.12.88)
文献５：KIBWAGE I. O., et al, 'Identification of novel erythromycin derivatives in mother liquor concentrates of Streptomyces erythraeus.' J. Antibiot., 1987, Vol.40, No.1, pages 1 to 6
文献６：EP, 937734, A1 (Solvay Pharmaceuticals G.m.b.H.)
25.8月.1999(25.08.99)
文献７：WO, 92/18134, A1 (Abbott Laboratories) 29.10月.1992(29.10.92)
文献８：EP, 349100, A2 (Lilly, Eli, and Co.) 3.1月.1990(03.01.90)

文献１及び２には、本願の請求の範囲１、２、２１並びに２４乃至２６記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.128:308701 及び DN.119:271625 のレコードにおける Registry Number 151052-42-5, 151052-43-6 及び 151122-18-8 が付与された化合物も参照されたい。)
文献３には、本願の請求の範囲３５並びに３７乃至３９記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.114:102696 のレコードにおける Registry Number 132201-81-1, 121590-61-2 及び 132137-36-1 が付与された化合物も参照されたい。)

(補充欄に続く)

補充欄（いずれかの欄の大きさが足りない場合に使用すること）

第　Ｖ　欄の続き

文献４には、本願の請求の範囲１、２４乃至２６、３５並びに３７乃至３９記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.111:58271 のレコードにおける Registry Number 105882-69-7, 105882-72-2 及び 121590-61-2 が付与された化合物も参照されたい。)
文献５には、本願の請求の範囲１、２並びに２４乃至２６記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.106:172535 のレコードにおける Registry Number 107745-55-1 及び 105882-69-7 が付与された化合物も参照されたい。)
文献６には、本願の請求の範囲１並びに２４乃至２６記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.131:144790 のレコードにおける Registry Number 236099-91-5 及び 151052-42-5 が付与された化合物も参照されたい。)
文献７には、本願の請求の範囲１並びに２４乃至２６記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.118:101716 のレコードにおける Registry Number 105882-69-7, 145692-88-2, 145692-89-3, 145692-94-0, 145692-95-1, 145692-97-3, 145693-00-1, 145693-01-2, 145693-02-3, 145693-03-4 及び 145774-00-1 が付与された化合物も参照されたい。)
文献８には、本願の請求の範囲１並びに２４乃至２６記載の発明であるシュードエリスロマイシン誘導体が記載されている。
(Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.113:59777 のレコードにおける Registry Number 105882-69-7, 127931-39-9 及び 127966-89-6 が付与された化合物も参照されたい。)
したがって、本願の請求の範囲１、２、２１、２４乃至２６、３５並びに３７乃至３９記載の発明は、新規性を有さない。

また、これら文献１乃至８における記載に鑑み、同等の効果を期待して末端の置換基を種々変更する程度のことは、当該技術分野における専門家が容易に想到し得るものである。したがって、本願の請求の範囲１乃至５２記載の発明は、進歩性を有しない。

本願の請求の範囲Ｉ乃至５２記載の発明は、産業上の利用可能性を有する。

EP・US

特　許　協　力　条　約

PCT

国際調査報告

（法８条、法施行規則第40、41条）
〔ＰＣＴ１８条、ＰＣＴ規則43、44〕

出願人又は代理人の書類記号	今後の手続きについては、国際調査報告の送付通知様式（ＰＣＴ／ＩＳＡ／２２０）及び下記５を参照すること。	
国際出願番号 ＰＣＴ／ＪＰ００／０５５０３	国際出願日 （日.月.年）　１７．０８．００	優先日 （日.月.年）
出願人（氏名又は名称） 社団法人北里研究所		

国際調査機関が作成したこの国際調査報告を法施行規則第41条（ＰＣＴ１８条）の規定に従い出願人に送付する。
この写しは国際事務局にも送付される。

この国際調査報告は、全部で　4　ページである。

☐ この調査報告に引用された先行技術文献の写しも添付されている。

１．国際調査報告の基礎

ａ．言語は、下記に示す場合を除くほか、この国際出願がされたものに基づき国際調査を行った。
☐ この国際調査機関に提出された国際出願の翻訳文に基づき国際調査を行った。

ｂ．この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際調査を行った。
☐ この国際出願に含まれる書面による配列表
☐ この国際出願と共に提出されたフレキシブルディスクによる配列表
☐ 出願後に、この国際調査機関に提出された書面による配列表
☐ 出願後に、この国際調査機関に提出されたフレキシブルディスクによる配列表
☐ 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった。
☐ 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

２．☐ 請求の範囲の一部の調査ができない（第Ｉ欄参照）。

３．☐ 発明の単一性が欠如している（第Ⅱ欄参照）。

４．発明の名称は
☒ 出願人が提出したものを承認する。
☐ 次に示すように国際調査機関が作成した。

５．要約は
☒ 出願人が提出したものを承認する。
☐ 第Ⅲ欄に示されているように、法施行規則第47条（ＰＣＴ規則38.2(b)）の規定により国際調査機関が作成した。出願人は、この国際調査報告の発送の日から１カ月以内にこの国際調査機関に意見を提出することができる。

６．要約書とともに公表される図は、
第 _____ 図とする。
☐ 出願人が示したとおりである。
☐ 出願人は図を示さなかった。
☐ 本図は発明の特徴を一層よく表している。
☒ なし

国際調査報告

国際出願番号 PCT／JP00／05503

A．　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int.Cl' C07H17/08 // A61K31/7048, A61P11/00, 29/00

B．　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int.Cl' C07H17/08 // A61K31/7048, A61P11/00, 29/00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS(STN), MEDLINE(STN),, EMBASE(STN)

C．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X / Y	EP, 838469, A (Solvay Pharmaceuticals G.m.b.H.) 29.4月.1998(29.04.98) & DE, 19644195, A & US, 5912235, A & JP, 10-130297, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN.128:308701 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1, 2, 21, 24-26 / 1-52

☒ Ｃ欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「Ａ」特に関連のある文献ではなく、一般的技術水準を示すもの
「Ｅ」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「Ｌ」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「Ｏ」口頭による開示、使用、展示等に言及する文献
「Ｐ」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「Ｔ」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「Ｘ」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Ｙ」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「＆」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
２４．１０．００	07.11.00

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００－８９１５ 東京都千代田区霞が関三丁目４番３号	森井　隆信 電話番号　０３－３５８１－１１０１　内線　３４５１	４Ｃ　９４５５

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（１９９８年７月）

C（続き）. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X / Y	EP, 550895, A1 (Kali-Chemie Pharma GmbH) 14.7月.1993(14.07.93) & DE, 4200145, A & US, 5418224, A & JP, 7-247299, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 119:271625 especially, compounds of RN:151052-42-5, 151052-43-6, 151122-18-8	1, 2, 21, 24-26 / 1-52
X / Y	EP, 382472, A2 (Lilly, Eli, and Co.) 16.8月.1990(16.08.90) & US, 5106961, A & JP, 2-240095, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 114:102696 especially, compounds of RN:132201-81-1, 121590-61-2, 132137-36-1	35, 37-39 / 1-52
X / Y	EP, 296717, A2 (Lilly, Eli, and Co.) 28.12月.1988(28.12.88) & JP, 63-307894, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 111:58271 especially, compounds of RN:105882-69-7, 105882-72-2 121590-61-2	1, 24-26, 35, 37-39 / 1-52
X / Y	KIBWAGE I. O., et al, 'Identification of novel erythromycin derivatives in mother liquor concentrates of Streptomyces erythraeus.' J. Antibiot., 1987, Vol. 40, No. 1, pages 1 to 6 & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 106:172535 especially, compounds of RN:107745-55-1, 105882-69-7	1, 2, 24-26 / 1-52
X / Y	EP, 937734, A1 (Solvay Pharmaceuticals G.m.b.H.) 25.8月.1999(25.08.99) & DE, 19805822, A & JP, 11-269193, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 131:144790 especially, compounds of RN:236099-91-5, 151052-42-5	1, 24-26 / 1-52
X / Y	WO, 92/18134, A1 (Abbott Laboratories) 29.10月.1992(29.10.92) & EP, 579770, A1 & JP, 6-509326, A & US, 5538961, A & US, 5523418, A & US, 5523401, A & US, 5554605, A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH, USA), DN. 118:101716 especially, compounds of RN:105882-69-7, 145692-88-2, 145692-89-3, 145692-94-0, 145692-95-1, 145692-97-3, 145693-00-1, 145693-01-2, 145693-02-3, 145693-03-4, 145774-00-1	1, 24-26 / 1-52

(続葉頁有り)

C（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X ／ Y	EP,349100,A2 (Lilly, Eli, and Co.) 3.1月.1990(03.01.90) & US,4920102,A & JP,1-311096,A & Database CAPLUS on STN, AMERICAN CHEMICAL SOCIETY (ACS), (Columbus, OH,USA), DN.113:59777 especially, compounds of RN:105882-69-7,127931-39-9, 127966-89-6	1,24-26 ／ 1-52